Sensitization in Neck Pain

a comparison between whiplashassociated disorders and mechanical neck pain subjects

Castaldo, Matteo

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

SENSITIZATION IN NECK PAIN

A COMPARISON BETWEEN WHIPLASHASSOCIATED DISORDERS AND MECHANICAL NECK PAIN SUBJECTS

BY
MATTEO CASTALDO

DISSERTATION SUBMITTED 2017

AALBORG UNIVERSITY
DENMARK

SENSITIZATION IN NECK PAIN: A COMPARISON BETWEEN WHIPLASH-ASSOCIATED DISORDERS AND MECHANICAL NECK PAIN SUBJECTS

PhD Thesis by

Matteo Castaldo

AALBORG UNIVERSITY
DENMARK

Center for Sensory-Motor Interaction,

Department of Health Science and Technology,

Aalborg University, Denmark

Dissertation submitted:	September 2017
PhD supervisor:	Prof. Lars Arendt-Nielsen, Aalborg University, Denmark
PhD committee:	Professor, PhD Michael Voigt Aalborg University, Denmark
	Professor Deborah Falla University of Birmingham,United Kingdom
	Professor, PhD Michele Sterling Griffith University, Australia
PhD Series:	Faculty of Medicine, Aalborg University
Department:	Department of Health Science and Technology

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-057-9

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

E-mail: matteo.castaldo@poliambulatoriofisiocenter.com

Printed in Denmark by Rosendahls, 2017

CV

Dr.Matteo Castaldo obtained his Bachelor in physical therapy at the University of Parma (Italy) in 2007.
After various manual therapy courses (Kaltenborn-Evjenth Concet, Ola Grimbsy Institute, Spinal Manipulation Institute, Ackermann Institute among others), has begun a distant part-time PhD program in 2011.
This activity is accompanied by a large clinical practice on neck pain and headache patients, and by a teaching activity (University of Parma, University of Siena, different course organizer).
Research activity has lead also to be involved in an international project on tension-type headache, called “Proof-of-concept study of a new technique for screening, diagnosing, and profiling patients with tension type headache”, at SMI®, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark.
Moreover, he is the head of Poliambulatorio Fisiocenter (Parma, Italy), a medical clinic in which he also treat patient with manual therapy and exercise therapy.
He is founding member of SIF (Italian Society of Physical Therapy), and member of AIFI (Italian Association of Physical Therapist).

ABSTRACT

Introduction: Neck pain represents one of the most frequent musculoskeletal disorders, with a huge impact in terms of health-care costs and subjects' disability. Sensitization mechanisms are claimed to play a role in whiplash associated disorders (WAD), while its relevance in mechanical neck pain (MNP) is still controversial.

Aim: To aims of the present PhD project were:

1) To compare distribution of TrPs in the suboccipitals, upper trapezius, levator scapulae, temporalis, supraspinatus, infraspinatus, deltoid and sternocleidomastoid muscles between subjects with WAD and MNP.
2) To investigate if manual therapy (MT) produces different effects between the two groups.
3) To investigate the relationship between clinical (neck pain intensity, neck-related disability, pain area) and psychophysical (quantitative sensory testing (QST) using pressure pain thresholds (PPTs)) outcomes in the two groups.
4) To evaluate the role of active TrPs on clinical and QST outcomes in the two groups as well as in a mixed neck pain subjects group.
5) To investigate the relationship between health history and sensitization in neck pain.

Studies: The difference in the distribution of TrPs in neck and shoulder muscles between WAD and MNP subjects was studied in the first paper. In the second one, the response to MT treatment in the two groups was studied. Then, correlations between clinical and psychophysical outcomes were studied in the two groups. The role of active TrPs on sensitization levels was also assessed. Finally, the role of health history (comorbid medical conditions, prolonged medication intake, surgical operations, comorbid musculoskeletal pain conditions) on sensitization in neck pain subjects was studied in the last paper.

Results: Active TrPs are more prominent in WAD than in MNP, which could confirm the idea that WAD subjects are more sensitized than MNP subjects (TrPs are claimed to be generators/perpetuating of sensitization mechanisms). Nevertheless, the WAD and MNP subjects exhibited similar improvements in the short term with MT treatments. Furthermore, the correlations between clinical and psychophysical outcomes were similar between the two groups, and in both groups

the presence of active TrPs was related to higher neck pain intensity, neck-related disability, and lower PPTs. Finally, in neck pain subjects, the duration of health history conditions was associated with lower PPTs (signs of sensitization).

Conclusions: Sensitization mechanisms, although not clearly diagnostically defined, may be present in both WAD and MNP patients, although greater signs of sensitization may be found in WAD patients. This does not necessary limits the response to MT treatment in the short term. Active TrPs seems to be associated with higher sensitization in patients in both groups. Health history should be investigated in the anamnesis, as this could reveal which patients are more prone to show sensitization features .

DANSK RESUMÈ

Indledning: Nakkesmerter er en af de mest hyppige lidelser i bevægeapparatet, de medfører en stor udgift for sundhedsvæsenet, ligesom de betyder funktionsnedsættelser hos den enkelte person. Det hævdes, at sensibiliseringsmekanismer spiller en rolle i piskesmældsrelaterede lidelser (whiplash-associated disorders, WAD), mens disse mekanismers indvirkning på mekaniske nakkesmerter (mechanical neck pain, MNP) stadig er omdiskuteret.

Formål: Formålet med denne ph.d.-afhandling er:

1) At sammenlige fordelingen af triggerpunkter i suboccipitale muskler, den øverste del af trapezius, levator scapulae, temporalis, supraspinatus, infraspinatus, deltoideus og sternocleidomastoid-musklerne hos patienter med henholdsvis WAD og MNP

2) At undersøge om manuel terapi (MT) har forskellig virkning hos de to grupper

3) At undersøge sammenhængen mellem kliniske (smerteintensitet, funktionsnedsættelser relateret til nakkesmerter og smerteudbredelse) og psykofysiske (kvantitativ sensorisk testning) målinger hos de to grupper med tryksmertetærskler som effekt

4) At vurdere aktive triggerpunkters betydning for kliniske målinger og kvantitative sensoriske tests hos såvel de to grupper som hos en gruppe af forsøgspersoner med blandede nakkesmerter

5) At undersøge sammenhængen mellem sygehistorie og sensibilisering

Studier: Det første studie undersøgte forskellen på fordelingen af triggerpunkter i nakke- og skuldermuskler hos WAD- og MNP-forsøgspersoner. Det næste studie undersøgte responsen til manuel terapi. Dernæst undersøgtes sammenhængen mellem resultaterne af de kliniske og psykofysiske tests for de to grupper. Hertil kom en vurdering af aktive triggerpunkters betydning for sensibiliseringsniveauerne. Endelig blev sygehistoriens (fx samtidige medicinske lidelser, vedvarende indtag af medicin, operationer eller samtidige lidelser i bevægeapparatet) betydning for sensibilisering hos patienter med nakkesmerter undersøgt.

Resultater: Aktive triggerpunkter er mere fremtrædende i WAD end i MNP, hvilket synes at bekræfte, at WAD-patienter er mere sensibiliserede end MNP-patienter (det hævdes at triggerpunkter genererer/vedligeholder sensibiliseringsmekanismer). Desuagtet udviste WAD- og MNP-patienterne ens forbedringer på kort sigt efter behandlinger med manuel terapi. Endvidere var korrelationen mellem kliniske og psykofysiske resultater ens for de to grupper, og i begge grupper kunne forekomsten af aktive triggerpunkter relateres til højere nakkesmerteintensitet, nakke-relateret funktionsnedsættelse og lavere tryksmertetærskler. Endelig var varigheden af sygdomsepisoder forbundet med lavere tryksmertetærskler (tegn på sensibilisering).

Konklusioner: Selvom sensibiliseringsmekanismer ikke er klart diagnostisk defineret, kan de være til stede hos både WAD- og MNP-patienter, selvom der kan findes større tegn på sensibilisering hos WAD-patienter. Dette begrænser ikke nødvendigvis responset til behandling med manuel terapi på kort sigt. Aktive triggerpunkter synes at være forbundet med højere sensibilisering hos begge grupper. Sygdomshistorien bør undersøges, da denne kan afsløre hvilke patienter, der er mere tilbøjelige til at udvise tegn på sensibilisering.

PREFACE

The studies have been conducted in the period 2012-2016 at the Center for Sensory Motor Interaction, Aalborg University, Denmark and at Poliambulatorio Dalla Rosa Prati, private practice, Parma, Italy.

This dissertation is based on the following papers, which are referred in the text as Paper I – IV:

I. Castaldo M, Ge HY, Chiarotto A, Villafañe JH, Arendt-Nielsen L. Myofascial trigger points in patients with whiplash-associated disorders and mechanical neck pain. Pain Med 2014; 15(5): 842-9

II. Castaldo M, Catena A, Chiarotto A, Fernández-de-Las-Peñas C, Arendt-Nielsen L. Do Subjects with Whiplash-Associated Disorders Respond Differently in the Short-Term to Manual Therapy and Exercise than Those with Mechanical Neck Pain? Pain Med 2018; 18 (4): 791-803

III. Castaldo M, Catena A, Chiarotto A, Villafañe JH, Fernández-de-las-Peñas C, Arendt-Nielsen L. Association between Clinical and Neurophysiological Outcomes in Patients with Mechanical Neck Pain and Whiplash-associated Disorders. Clin J Pain. 2017 Jul 3 [Epub ahead of print]

IV. Castaldo M, Catena A, Fernández-de-las-Peñas C, Arendt-Nielsen L. Widespread pressure pain hypersensitivity, health history, and trigger points in patients with mechanical and traumatic neck pain: an explorative study

ACKNOWLEDGEMENTS

This thesis is based on the work which has been done in the last five years with the support from a number of people to whom I am most thankful and wish to express my gratitude.
First of all, Professor Lars Arendt-Nielsen, the supervisor of the thesis, which has supported and helped me with his impressive knowledge from the beginning of this new development of my career. With his encouragement, suggestions, and patience he has helped me in going in the right direction and provided a constant stimulation to work at the best of my possibilities.
I would also thank my co-authors, Prof. Hong-You Ge that has sadly passed away, Dr. Alessandro Chiarotto, Dr. Jorge Hugo Villafañe, Dr. Antonella Catena (she needs a special thank for the last-minute work), and Prof. Cesar Fernández-de-las-Peñas; all of them have added an important contribution to the present research, and it has been a pleasure to collaborate with them.
Special thanks are dedicated to my girlfriend Monica, as she has been a very important figure in the last years, sustaining and supporting particularly in the most difficult times.
I'm also thankful to all my friends and to my family, for supporting me and tolerating the huge amount of time (nights and week-ends) I dedicated to this project instead of being with them in the last years.
The last thought is for Mattia, this result is dedicated to you, as you guided me every day, and I know you would be proud of me and we would be celebrating this together my friend.

TABLE OF CONTENTS

ABBREVIATIONS

WAD: whiplash-associated disorders

MNP: mechanical neck pain

CS: central sensitization

TrPs: trigger points

MT: manual therapy

QST: quantitative sensory testing

PPTs: pressure pain thresholds

IASP: international association for the study of pain

CNS: central nervous system

QTF: Quebec task force

NPRS: numeric pain rating scale

NDI: neck disability index

LTR: local twitch response

ACh: acethylcoline

IC: ischemic compression

NSAIDs: nonsteroideal anti-inflammatory drugs

EMG: electromyography

ROM: range of motion

1. INTRODUCTION

1.1 Background

Neck pain is considered as one of the most frequent complaints in the general population, it is the fourth leading cause of disability, and it has a 12-month prevalence of 30%-50% (Hogg-Johnson et al., 2008).
It's a condition that tends to be recurrent or persistent, with up to 85% of people suffering from ongoing pain for many years after the first episode (Carroll et al., 2008).
It's nature is often chronic episodic, with episodes occurring with some periods of recovery in between episodes (Hoy et al., 2014).
Specific serious pathology (e.g. tumors, infections, spinal pathology) may provoke neck pain, but they goes beyond the scope of the present project and will not be discussed.
The present project studied two very common neck pain populations: 1) subjects with whiplash-associated disorders (WAD) (i.e. traumatic neck pain), and 2) subjects with mechanical neck pain (MNP) (i.e. nonspecific or idiopathic neck pain). These two groups of neck pain subjects, have a different pathogenesis, and different as well as common mechanisms may be underlying these two pain conditions. Increasing evidence suggests that the clinical picture of neck pain subjects may be very different between different subjects, and many factors may influence it (e.g. physical factors, psychological factors, sensitization mechanisms, environment). However, a better understanding of the signs, symptoms, and mechanisms underlying neck pain conditions is necessary, to convey novel findings from clinical and experimental neck pain studies to the clinical setting, improving the quality of assessment and treatment of this very common pain condition.

1.2 Aims of the project

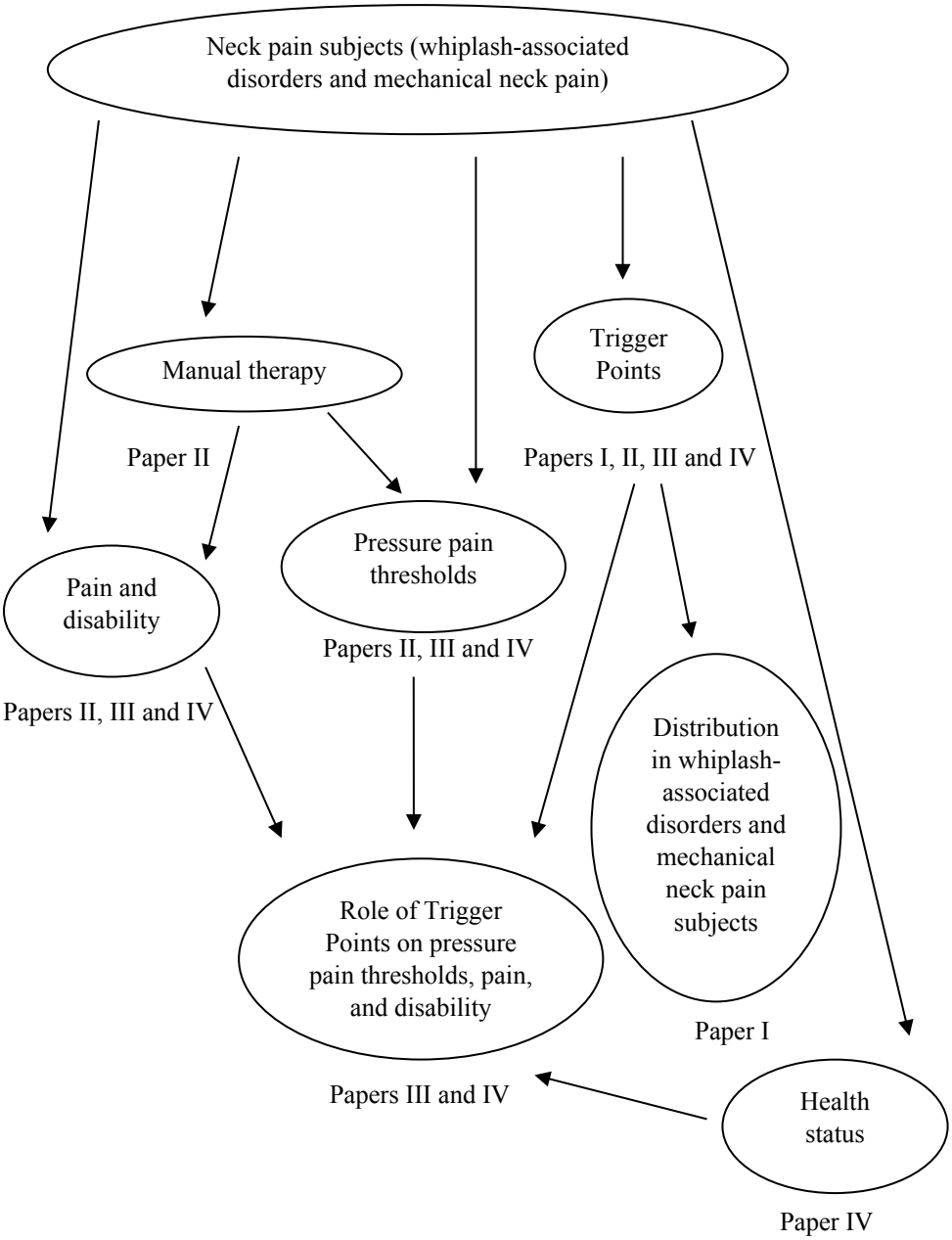
In WAD and MNP most of the signs and symptoms experienced by subjects affected by neck pain are commons (neck/arm pain, headache, dizziness, shoulder pain, stiffness, numbness, sleeping difficulties, fatigue and cognitive deficits) (Hogg-Johnson et al., 2008), but the severity of symptoms may be influenced by the degree of sensitization of the pain system. In WAD subjects evidence support the presence of central sensitization (CS), while in MNP subjects more conflicting results are

found (Johansen et al., 1999, Curatolo et al., 2001, Sterling et al., 2003a, Malfliet et al., 2015, Javanshir et al., 2010, Stone et al.,2013).
Many aspect of neck pain may have a relationship with the degree of sensitization: the peripheral nociceptive input (e.g. Trigger Points (TrPs), zygapophyseal joints), the clinical presentation (neck pain intensity, neck-related disability, pain area), the response to treatment (e.g. manual therapy (MT) and exercises), psychological factors, and the general health status (prolonged medications intake, comorbid medical conditions, comorbid musculoskeletal pain conditions, previous surgical operations).
The aims of the present PhD project were:

1) To compare distribution of TrPs in the suboccipitals, upper trapezius, levator scapulae, temporalis, supraspinatus, infraspinatus, deltoid and sternocleidomastoid muscles between subjects with WAD and MNP.
2) To investigate if MT produces different effects between the two groups.
3) To investigate the relationship between clinical (neck pain intensity, neck-related disability, pain area) and psychophysical (quantitative sensory testing (QST) using pressure pain thresholds (PPTs)) outcomes in the two groups.
4) To evaluate the role of active TrPs on clinical and QST outcomes in the two groups as well as in a mixed neck pain subjects group.
5) To investigate the relationship between health history and sensitization in neck pain.

Figure 1 summarizes the outline of the research project.

Figure 1. The outline of the research project



2. NECK PAIN

2.1 Epidemiology

Neck pain is considered to be an unpleasant sensory and emotional experience in the region of the neck, associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk, 1994).
Burden of disease rankings are based on how much death and disability causes each disease, and neck pain is classified as the 4th cause of years lived with disability by the Global Burden of Disease studies GBD (Hoy et al., 2014), and a recent update from the same group concluded that lower back and neck pain was the leading global cause of disability in 2015 in most countries (Vos et al., 2016).
It represents one of the most frequent musculoskeletal disorders, second only to low back pain in terms of cost and prevalence (Ferrari and Russell, 2003, Childs et al., 2011), increasing in both the general population and specific occupational groups (Hogg-Johnson et al., 2008) and with a major socio-economical impact with substantive direct and indirect costs (Borghouts et al.1996, Korthals-de Bos et al. 2001).
In fact, neck pain seems to be more common among lower socio-economics status groups, in subjects performing repetitive, static or physically demanding work, those with previous neck trauma, and among those suffering from depression and headache (Cotè et al., 2003).
Further, women seems to have a higher prevalence of neck pain (Haldeman et al., 2010), and getting older does not seem to increase the chance of development of neck pain (Fejer and Leboeuf-Yde, 2012).
Neck pain is usually first experienced in childhood or adolescence (Ståhl et al., 2004, Vikat et al., 2000), and it is associated with high rates of recurrence (Luime at al. 2005, Bot et al., 2005), and chronicity (Childs et al., 2011).
Its impact on individuals every-day life is huge, as subjects may have difficulties with driving a car, turning the head, working on a computer (Haldeman et al., 2010; Guzman et al., 2008), and in having a normal ability to participate in work, social and sporting environment (Manchikanti et al., 2009).
Its annual prevalence (number of individuals with a disease at a given time point) among the general and workforce populations is of 30% to 50% (Hogg-Johnson et al., 2008), this variability is partially due to the considerable methodological heterogeneity (e.g. case definition, recall period used, age and sex distribution, sample size, diagnostic criteria) across studies.

A systematic review concluded that genetics, poor psychological health, and exposure to tobacco are risk factors for neck pain, and that disc degeneration was not a risk factor, casting doubts on the importance of the tissue damage on the development of neck pain (Hogg-Johnson et al., 2008).
Further, a history of low back pain, poor self-assessed health, poor psychological status (Hogg-Johnson et al., 2008, Carroll et al., 2008), low job satisfaction, sedentary work postures, a bad work environment (e.g. mouse position or seat position), ethnicity, smoking (Haldeman et al., 2010, Cotè et al., 2008) have been found to be associated with the onset of neck pain.
The estimated 1-year incidence (number of new cases of a disease in a given time period) from available studies ranges between 10.4% and 21.3% (Ehrmann et al., 2002, Ståhl et al., 2004) with a higher incidence in office and computer workers (Cotè et al., 2008).
A previous review of the course and prognosis of neck pain found that 50-85% of individuals which experience an episode of acute neck pain, will report neck pain 1-5 years later (Carroll et al., 2008).
It's often characterized by exacerbations, and more than one third of patients with neck pain will develop chronic symptoms (Cotè et al., 2004), substantially increasing health care costs, work absenteeism, and loss of productivity (Cotè et al., 2008).
An important finding that can help in understanding why so many patients with neck pain or low back pain develop chronic or recurrent pain, may be that with pain resolution, the muscle function does not recover spontaneously, but needs to be specifically re-educated (Sterling et al., 2003b).
Factors associated with poor outcomes include previous neck injury, high pain intensity, self perceived poor general health, fear avoidance, and getting angry or frustrated (Carroll et al., 2008).

2.2 Aetiology

Interpretation of neck pain studies is complicated, as there is a huge variation in the way neck pain is classified in the literature, with more than 300 definitions for neck pain, differences regarding the considered anatomical region (e.g. 'neck', 'neck and shoulder', 'neck and upper thoracic'), or the recall period used (e.g. 'current neck pain', 'one-year', ' lifetime') (Guzman et al., 2008).
Different tissues and structures (e.g. muscles, joints, nerves, discs, ligaments) may be involved in neck pain, and they can be irritated or injured by a trauma, poor posture, mechanical stress, or repetitive movements (Carroll et al., 2009).

Often it has a multifactorial aetiology, with non-modificable risk factors (i.e. age, sex, genetics), and modificable risk factors (e.g. smoking, psychological aspects, type of work, physical activity participation). Common degenerative structural changes are not considered a risk factor for the development of neck pain (Haldeman et al., 2010).

Nevertheless, often the source of neck pain is often not identifiable, and when structural abnormalities are found (e.g. joint degeneration, intervertebral disc space narrowing, spondylosis), they are more related to aging than to clinical presentation (considered physiological aging degeneration) (Haldeman et al., 2010).

Furthermore, often no underlying structural pathology is usually found (Sheather-Reid and Cohen, 1998) and many environmental, personal, psychosocial factors may influence the onset and the development of neck pain (Guzman et al., 2008, Haldeman et al., 2010).

All these factors may contribute to the overall clinical picture, and it can be hard to ascertain which tissue is the responsible of the symptoms experienced by the subject (Apkarian et al., 2009).

In absence of a previous neck trauma, the aetiology of chronic neck pain is non-specific, and it is not associated with tissue pathology (Bogduk, 1999), but more related to neck dysfunction, psychological status, social status, poor posture, and increased activation of the neck and shoulder muscle resulting in higher levels of mechanical loading on the cervical spine (Szeto et al., 2005).

Despite the huge variability of neck pain classification in the literature, in the present project were considered neck pain subjects presenting with neck/shoulder pain with cervical symptoms provoked by sustained neck postures, neck movements, or palpation of the cervical spine.

At the time of assessment/treatment, the assessor was blinded to subjects history of neck pain. Subsequently, subjects were divided into WAD or MNP according to their history of neck pain, after that all assessment/treatment had been performed.

All neck pain subjects were chronic, included regardless the degree of chronicity of neck pain, but they had to be symptomatic since at least 3 months at the time of evaluation. This gave a final result of two sample of neck pain subjects (WAD and MNP) of various symptoms duration, similar to what is often seen in every day practice . In fact, many subjects with neck pain, reports symptoms since a long period, with or without period of remission between acute phases.

When peripheral tissues are damaged, overloaded, or inflamated, nociceptive and non-nociceptive informations arising from these tissues undergo modulation in the central nervous system (CNS).

As in many other musculoskeletal pain syndrome, central hypersensitivity may play an important role in the development of chronic neck pain (Nijs et al., 2010): the

pain may persist after normal tissue healing, without any nociceptive input, or be exaggerated in relation to the nociceptive input.
This can be a possible explanation the low correlation between symptoms and tissue damage/pathology often present in neck pain subjects: a better understanding of the role of sensitization mechanisms on neck pain and which factors may drive pain sensitization has been studied in the present thesis.
According to the International Association for the Study of Pain (IASP), peripheral sensitization is defined as: "Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields" and the definition of CS is, "Increased responsiveness of nociceptive neurons in the CNS to their normal or sub-threshold afferent input" (Merskey and Bogduk, 1994).
The term "central sensitization" may for many purposes be a too broad term from a mechanistic point of view as "central" may refer to (1) ipsilateral sensitization associated with the local nociceptive focus, (2) segmental sensitization contralateral to the local nociceptive focus, (3) extraterritorial spreading sensitization around local nociceptive focus, or (4) generalised widespread sensitization. In the following text the broader terminology "central sensitization" may be used referring to central hypersensitivity.

2.3 Whiplash-associated disorders (WAD)

Whiplash is an acceleration-deceleration mechanism of energy transfer to the neck, which is usually a result of rear-end or side-impact motor vehicle collisions, but can also occur from other injury types (Spitzer, 1995).
The various symptoms experienced by people involved in such injuries, is called WAD, and represent a large public health problem associated with high socio-economic costs (Spitzer, 1995), as the number of subjects presenting WADs related to motor-vehicle accidents has been increasing over the last 30 years (Haldeman et al., 2010).
The Quebec Task Force (QTF) developed a classification system of WAD, in which patients are classified from grade 0 to IV, going from no complaints and no physical signs, to fracture in the neck (Spitzer, 1995) (**Table 1**).
The most common symptoms in whiplash patients are neck/arm pain, headache, dizziness, stiffness, numbness, sleeping difficulties, tinnitus, fatigue and cognitive deficits (Spitzer, 1995, Manchikanti et al., 2009), and due to such a variability of symptoms not isolated in the neck, it can be considered a general illness instead of a local condition (Ferrari et al., 2005).
Recover tends to happen in the first 3 months after injury, with little improvement following this first stage (Sterling et al., 2010). Different factors associated with

poor recovery have been identified: high initial neck pain intensity and neck-related disability, catastrophizing, age, post-traumatic stress symptoms, low self-efficacy and cold hyperalgesia (Goldsmith et al., 2012, Walton et al., 2013; Ritchie and Sterling, 2016), and validated (Sterling et al., 2012).
In fact, there is a large proportion of subjects (around 50%) which develops chronic symptoms up to a year following injury (Carroll et al., 2008).
This is often not related with the tissue injury itself, but is more related to dysfunction of the pain processing system, which may cause exaggerated pain responses which can persist even after removal of the peripheral noxious input or healing of the injured tissue (Curatolo et al., 2011a).
Further, if tissue lesion is present, does not necessary mean that this (i.e. facet joints, intervertebral discs, vertebral artery, dorsal root ganglia and muscles) is causing the symptoms: clinical research on the association between tissue lesion and symptoms is lacking (except for facet joints, which have been identified as a possible source of pain after whiplash (Lord et al., 1996)).
Furthermore, in more than 90% of WAD subjects it's not possible to identify an organic pathology (Ferrari et al., 2015), and supporting this, the intensity of trauma (i.e. the amount of force transmitted to neck tissues) has been proven not to have a relationship with the symptoms presentation (Carroll et al., 2008).
Therefore, the classical biomedical model can't explain why so many subjects develop chronic pain after whiplash in the absence of evident tissue damage or lesion (Dommerholt, 2005, Curatolo et al., 2011a), but a biopsychosocial considering also psychological, behavioral, social factors in addition to biomedical ones (Ferrari and Russell, 1997).
In chronic WAD there are changes in the pain processing mechanisms, including hypersensitivity to a variety of stimuli, including mechanical, electrocutaneous stimulation, and induced muscle pain, which may all be manifestations of changes in central pain processing (Johansen et al., 1999, Curatolo et al., 2001, Sterling et al., 2003a, Van Oosterwijck et al., 2013).
Changes in central pain processing may occur even soon after injury, as subjects with persistent pain (at 6 months post-trauma) showed signs of generalized hypersensitivity within the first month post-trauma (Sterling et al., 2003a).
Peripheral nociceptive input (injury, overload, inflammation) seems to be necessary to initiate/maintain CNS hypersensitivity (Baron et al., 2013): zygopophyseal joints and TrPs in neck and shoulder muscles may be source of pain after whiplash (Lord et al., 1996, Gerwin et al., 1998).
In the present project TrPs have been investigated, as they have been found to perpetuate lowered pain thresholds in uninjured tissue (signs of central hypersensitivity), which can be immediately (and temporary) normalized anestitizing the TrPs, even in chronic whiplash (Freeman et al., 2009).

In all the four papers on which is based this thesis, a mixed sample of WAD subjects were included if they met the QTF criteria for classification of Grade I or II (**Table 2**), which represents more than 90% of WAD subjects (Spitzer 1995).
Exclusion criteria were: 1) previous history of neck surgery; 2) any therapeutic intervention for the cervical spine in the previous 3 months; 3) red flag (e.g. infections, malignancy, fracture, rheumatoid arthritis or osteoporosis); 4) QTF Grade 0,III,IV; and, 5) diagnosis of fibromyalgia according to the American College of Rheumatology.

Table 1.The Quebec Task Force Classification (QTFC) for Whiplash (Spitzer, 1995)

QTF classification grade	**Clinical presentation**
0	No complaint about neck pain No physical signs
I	Neck complaints of pain, stiffness or tenderness only No physical signs
II	Neck complaints Musculoskeletal signs including: - Decreased ROM - Point tenderness
III	Neck complaint Musculoskeletal signs Neurological signs including: - Decresead or absent deep tendon reflexes - Muscle weakness - Sensory deficits
IV	Neck complaint and fracture or dislocation

2.4 Mechanical neck pain (MNP)

MNP (also called nonspecific or idiopathic), affects 45-54% of the general population at some time during their lives, and it has a multi-factorial origin including one or more of the following: poor posture, anxiety, depression, or neck strain (Hoy et al., 2014).
It's prevalence is greater with increasing age, and peaks in middle-aged individuals, with women affected twice often as man (Hogg-Johnson et al., 2008).
Most of the symptoms in MNP (neck/arm pain, headache, dizziness, shoulder pain stiffness, numbness, sleeping difficulties, fatigue and cognitive deficits) are the same that can be found also in WAD subjects (Hogg-Johnson et al., 2008).
A systematic review found an association between physical exposures at workplace (i.e. the mechanical load) and the development of neck pain: repetitive movements, work posture, computer work may all be risk factors (Mayer et al., 2012).
Risk factors for delayed non-recovery include older age, and history of other musculoskeletal disorders (Walton et al., 2013).
The exact pathology of MNP is not known, and different anatomical structures may be involved, including intervertebral joints, neural tissues, discs, muscular disorders.
As reported in WAD, TrPs may be pain generators also in this neck pain population: MNP subjects presents with more active TrPs in neck muscles than healthy controls, and no difference is found for latent TrPs (Fernández-de-las-Peñas et al., 2007a), being latent TrPs commonly found in health subjects (Chaiamnuay et al., 1998).
In MNP, local pressure pain hypersensitivity in the cervical area is normally found (Scott et al., 2005, La Touche et al., 2010, Johnston et al., 2008a), suggesting peripheral mechanisms.
If in WAD subjects there is also evidence of central pain processing anomalies (Sterling et al., 2003a, Curatolo et al., 2001, Kasch et al., 2005, Banic et al., 2004, Freeman et al., 2009), in MNP the literature shows unclear evidence about central pain processing anomalies.
A recent systematic review on CS in subjects with chronic idiopathic neck pain, concluded that results from the available studies provide an inconclusive message, and that CS is not a major characteristic feature of these subjects, but it can be present in some individuals. Their conclusion was that in the future subgroup of MNP subjects with signs of CS should be defined (Malfliet et al., 2015).
In fact, some studies found that signs of CS are present in chronic WAD but not in chronic idiopathic neck pain (Coppieters et al., 2015, Scott et al., 2005, Chien and Sterling, 2010), while other authors found some degree of CS also in MNP (Javanshir et al., 2010, Johnston et al., 2008a).

The main difficult is comparing the results of these studies as they have different inclusion/exclusion criteria, used different methods for assessing CS, different sample size, and different pain and disability levels of the subjects.
For example, in the study of Javanshir et al. (2010) chronic neck pain subjects had low pain and disability levels, and the sample size was very small.
In the study of Chien and Sterling (2010) signs of CS were not found in idiopathic neck pain subjects; these subjects were chronic (>3 months of neck pain), but neck pain duration longer than 3 years was an exclusion criteria: many chronic idiopathic neck pain subjects have a longer history of neck complaints which may be related with more sensitization, and for that reason in the present project were included also subjects with longer history of neck pain.
The role of pain duration in the development of CS in chronic MNP subjects has been investigated also by La Touche et al. (2010), and by Javanshir et al. (2010) which found that widespread pressure pain hypersensitivity was not a feature in subjects with acute MNP, but was present in some subjects with chronic MNP.
Chronic idiopathic neck pain is episodic in nature, and this may lead to an interruption in nociceptive input, which may limit/prevent the development of the pathological behavior of the CNS (Guzman et al., 2008). Some subjects may have a more continue pain, and thus become a sub-groups of subjects with chronic idiopathic neck pain with greater signs of CS.
In fact, it is necessary to remember that CS is not an "all or nothing" phenomenon, but rather a continuum of altered pain processing mechanisms (Chien and Sterling., 2010).
A recent study, reported that subjects with chronic nonspecific neck pain showed signs of peripheral sensitization compared to healthy subjecst, but only subjects with chronic nonspecific neck pain with neuropathic features showed signs of CS: this could suggest different mechanisms of pain processing between chronic nonspecific neck pain subjects with/without neuropathic features (Lopez-de-Uralde-Villanueva et al., 2016).
However, regardless the degree of sensitization, both traumatic and nontraumatic subjects may present with reduced ROM, altered muscle recruitment patterns, morphological changes in neck muscles, and sensorimotor disturbances (Treleaven, 2008, Sterling et al., 2003b, Elliott et al., 2011).
Subjects presenting with neck/shoulder pain with cervical symptoms provoked by sustained neck postures, neck movements, or palpation of the cervical spine were included in this group.
Exclusion criteria were: 1) a history of whiplash trauma; 2) previous history of neck surgery; 3) any therapeutic intervention for the cervical spine in the previous 3 months; 4) red flag (e.g. infections, malignancy, fracture, rheumatoid arthritis or

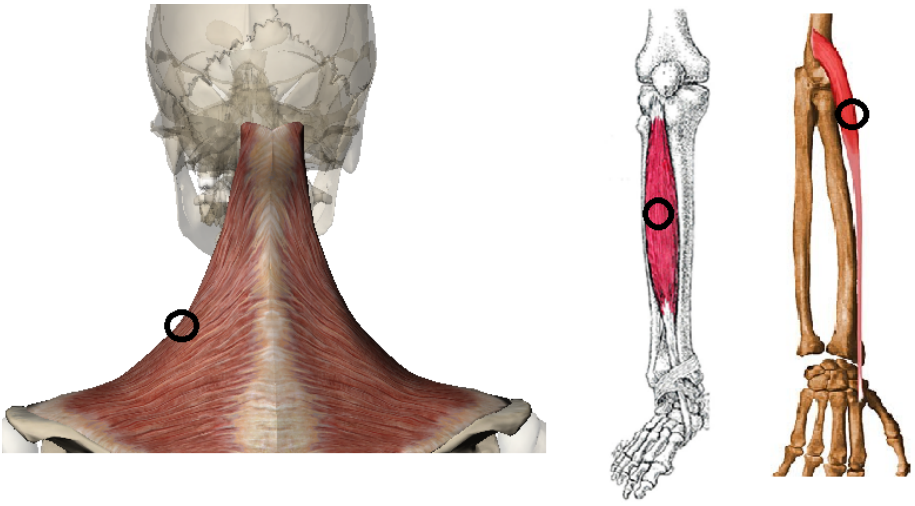
osteoporosis); or, 5) diagnosis of fibromyalgia according to the American College of Rheumatology.

2.5 Assessment of neck pain subjects

There are a variety of tools to quantify neck pain, especially self-report questionnaires which detect the current level of pain and disability.
The Visual Analogue Scale, the Numeric Pain Rating Scale (NPRS) are commonly used to measure pain intensity, while the Neck Disability Index (NDI) is usually used to measure disability.
To measure pain area extension is often used a body chart, in which the patient draw the area of pain, which can be then digitized in order to obtain a numeric value.
Mechanical hypersensitivity may be assessed with various QST: pressure pain threshold (PPT) is commonly used, and it is defined as "the minimal amount of pressure applied needed to evoke a sensation of pain"; it is usually assessed with a digital (or manual) algometer (Somedic AB, Söstala, Sweden) in order to obtain information about local and widespread pressure pain hypersensitivity (assessing healthy body location far away from the pain area) (Chesterton et al., 2007).
In the present papers neck-related disability was assessed with the NDI, neck pain intensity with the NPRS, spontaneous pain area extension with a body chart, and local and widespread pressure pain hypersensitivity with PPTs over different locations.
To assess neck-related disability, it was used the Italian version of NDI (Monticone et al., 2012), which is a self-report questionnaire that consists of 10 items concerning daily living, pain and concentration (Vernon and Mior, 1991). Each item is scored from 0 to 5, with 0 indicating no disability and 5 indicating full disability.
The total score ranged from 0 to 50, and it was transformed in a percentage from 0 to 100%, where high values represented high disability.
The NDI was chosen because it is the most frequently applied questionnaire for patients with neck pain. Furthermore, it is considered a reliable tool and demonstrated construct validity (Vernon and Mior, 1991), in patients with chronic neck pain, cervical radiculopathy, and WAD (Schellingerhout et al., 2012).
A systematic review concluded that a minimum clinically important difference of at least 7 points from a total of 50 is required to be clinically meaningful (MacDermid et al., 2009).
To measure pain intensity, it was used a NPRS, in which subjects had to rate the intensity of neck pain on an 11-point numerical pain rating scale (0:no pain, 10: maximum pain) (Cleland et al., 2008, Schellingerhout et al., 2012). This scale is an uni-dimensional measure of the perceived intensity of pain (Jensen et al., 1986), and

a paper investigating it's psychometric properties concluded supporting its use (Kahl and Cleland et al., 2005), showing adequate responsiveness and fair to moderate test-retest reliability (Cleland et al., 2008).
The minimal detectable change and minimum clinically important difference for NPRS in patients with neck pain have been reported as 1.3 and 2 points, respectively (Cleland et al., 2008).
To measure pain area extension, subjects were asked to draw the distribution of their pain symptoms on an anatomical body map. The drawn area was then measured with a digitizer (ACECAD D9000, Taiwan), and analyzed with Vistametrix software (SkillCrest, USA, LLC) (Lee et al., 2005, Toomingas et al., 1999).
Pain drawings are often used in both research and clinical settings, and are considered a reliable tool (Roach et al., 1997, Ohnmeiss, 2000).
PPTs were assessed over upper trapezius muscle (halfway between occiput and acromion), over tibialis anterior muscle (in the middle of the muscle), and over extensor carpi radialis longus muscle (2-3 cm distally from the lateral epicondyle) (**Figure 2**).
Walton et al. (2011) reported that PPTs over neck area assessed with an algometer exhibited good to excellent reliability and a minimal detectable change of 47.2 kPa over the neck and of 97.9 over tibialis anterior muscle in subjects with acute neck pain, and their measurement is widely used in the clinic and in the scientific field (Waller et al., 2015).

Figure 2. PPTs assessment point in upper trapezius (A), tibialis anterior (B), and extensor carpi radialis longus (C) muscles.



A B C

PPTs: pressure pain thresholds

In paper I, no significant differences for pain area (P=0.05) and pain intensity (P=0.13) between MNP and WAD subjects were found. Pain area difference was almost significant, with the WAD group presenting a greater extension of pain area, and higher pain intensity. Neck-related disability and PPTs were not investigated in this paper.

In paper II, WAD subjects exhibited higher neck-related disability (P=0.021), larger extension of pain area (P=0.003), and lower PPTs in the tibialis anterior muscle (P=0.009) than MNP subjects. No significant difference for pain intensity was found, although it was higher in WAD subjects, and for PPTs in upper trapezius mucles, although it was lower in WAD subjects. These findings may underlie a greater degree of CS in WAD subjects in this paper.

In paper III, no significant differences for pain area, pain intensity, neck-related disability, and PPTs were found between WAD and MNP subjects; although individuals with WAD tended to exhibit higher neck-related disability, larger pain area, higher intensity of neck pain, and lower PPTs (all, P>0.061).

Finally, also in paper IV no significant differences for pain area, pain intensity, neck-related disability, and PPTs (all, P>0.12) were found between WAD and MNP subjects; however this time MNP subjects exhibited higher neck pain intensity and neck-related disability, and lowered PPTs.

The main finding from the four papers, is that MNP and WAD populations may present with a large variability of the clinical presentation, although WAD subjects showed a general tendency to show higher pain intensity, neck-related disability, greater pain area extension, and lowered PPTs (which may all underlie higher degree of sensitization), it is also possible to find MNP subjects showing higher sensitization than WAD subjects (although the difference was not significant), or having populations of WAD and MNP subjects with similar characteristics.
In previous studies pain intensity has been found to be similar between the two groups (Coppietiers et al., 2015), higher disability and lower PPTs at a distant site have been found in WAD, but similar PPTs over neck region (Chien and Sterling, 2010, Scott et al., 2005).
Different inclusion/exclusion criteria, sample size, diagnostic criteria, degree of chronicity, may all partially explain the differences found in the present research project.
In fact, the role of time in the development of CS has already been studied, and it may be that MNP subjects with a long history of neck complaints may gradually develop features of CS related to the continuous nociceptive input from the periphery. The time necessary to this progressive sensitization is still unclear (Graven-Nielsen and Arendt-Nielsen 2010).
The findings from these four different samples of neck pain subjects, support the thesis that the clinical presentation and the widespread pressure pain hypersensitivity of neck pain subjects may be very heterogeneous, regardless the origin of neck pain (although greater signs may normally be found in WAD subjects), and specific sub-groups of MNP subjects with signs of CS may be present.
Table 2 summarizes demographic, clinical and psychophysical characteristics of subjects from the four papers.

Table 2. Demographic, clinical and psychophysical characteristics of subjects from the four papers

Table 2	MNP paper I	WAD paper I	MNP paper II	WAD paper II	MNP paper III	WAD paper III	MNP paper IV	WAD paper IV
Sex (female/ male)	33/23	28/21	16/6	25/3	36/10	43/8	23/11	26/8
Age (years)	45.2 ± 1.8	41.6 ± 1.7	44 ± 13	43 ± 13	43 ± 13	43 ± 12	43 ± 12	40 ± 11.5
NPRS (0-10)	4.7 ± 0.4	5.6 ± 0.4	2.9 ± 2.8	4.1 ± 2.1	3.5 ± 2.9	3.7 ± 2.5	4.8 ± 3	4.6 ± 2.8
NDI (%)	NA	NA	**21.0 ± 12.1***	**28.8 ± 10.9***	23.7 ±	29.4 ± 14.1	25.8 ± 12.7	23.1 ± 11.5
Pain area (AU)	3506.7 ± 341.8	4521.8 ± 326.7	**1614.3 ± 999.4***	**2700.1 ± 1370..5***	1972 ± 1612	2622 ± 1758	2972.2 ± 4987.7	2745.7 ± 1620.7
PPT upper trapezius (kPa)	NA	NA	307.4 ± 142.3	263.1 ± 118.6	305 ± 140.1	294.1 ± 178.6	226.1 ± 83.7	244.19 ± 110.2
PPT tibialis anterior (kPa)	NA	NA	**453.2 ± 196.5***	**325.2 ± 137.2***	441.6 ± 201.8	392.3 ± 240.6	349.4 ± 174.9	360 ± 146.8
PPT extensor carpi radialis longus (kPa)	NA	NA	NA	NA	NA	NA	214.9 ± 105.7	191.74 ± 77.8

MNP: mechanical neck pain; WAD: whiplash associated disorders; NPRS: numeric pain rating scale; NDI: neck disability index; AU: arbitrary units; PPT: pressure pain thresholds; kPa: kilopascal; NA: not available

Data are expressed as mean ± standard deviation (95% confidence interval)

*Significant differences ($P<0.05$) between groups in paper II

The associations between neck pain intensity, neck-related disability, pain area, and PPTs in WAD and MNP subjects were studied in paper III.

A small to moderate positive significant association between pain and disability was found in both WAD subjects (r_s=0.406; P=0.003) and MNP subjects (r_s=0.544; P<0.001): the higher the intensity of neck pain, the higher the disability.

At the same time, it is important to remember that pain and disability assessment may both be influenced by physiological, psychosocial, and environmental factors (Von Korff et al., 1992), and should always be considered and measured as two different aspects to avoid the risk of overlooking specific groups of subjects (Leboeuf-Yde et al., 2001).

Further, a small to moderate positive significant association between pain area and disability was found in MNP subjects (r_s=0.314; P=0.034), but not in WAD subjects (r_s=0.261; P=0.065), although it was close to significant also in WAD subjects: the larger the pain area extension, the higher the disability, as recently found by Ris et al (2016), which found a positive association between pain area and disability in a mixed sample of traumatic and non-traumatic chronic neck pain subjects.

Significantly small to moderate negative associations between pain and PPTs (both local and distant) were found in both MNP (local: r_s=-0.397; P=0.008; distant r_s=-0.365; P=0.015), and in WAD subjects (local: r_s=-0.290; P=0.041; distant: r_s=-0.294; P=0.038): the higher the pain experienced by subjects, the lower the PPTs.

Statistically a small to moderate negative significant association between neck-related disability and local PPTs was found in both MNP (r_s=-0.397; P=0.006), and in WAD subjects (local: r_s=-0.380; P=0.006): the higher the neck-related disability, the lower the local PPTs.

Finally, a small to moderate negative significant association between neck-related disability and distant PPTs was found in MNP subjects (r_s=-0.428; P=0.003), but not in WAD subjects (r_s=-0.255; P=0.112): the higher the neck-related disability, the lower the distant PPTs.

Previous papers found conflicting results (Kamper et al., 2011, Herren-Gerber et al., 2004, Farasyn and Meeusen, 2005, Imamura et al., 2016), and a systematic review (Hübscher et al., 2013) concluded that the associations between PPTs, pain, and disability in spinal pain syndromes are weak and future studies are needed. None of them compared these associations between WAD and MNP.

The findings of paper III support the idea that these associations may be very similar between the two groups of neck pain subjects, but at the same time it is mandatory to remember that our two groups had very similar clinical presentation and PPTs values.

It may be concluded that the relationship between clinical and psychophysical outcomes is similar in neck pain, at least when these two categories of neck pain subjects does not present with different degree of CS.

2.6 Current management strategies

The clinical management of neck pain can be complex and may involve multimodal care to address its symptoms and consequences (Sutton et al., 2016).
Kelly et al. (2016) in a recent systematic review, concluded that clinical prediction rules for neck pain are still at the initial stages and not validated or undergone to impact analysis, so their clinical use is not yet suggested, but progress is made towards sub-grouping subjects which may need different management strategies.
Recent guidelines for the management of acute neck pain (both WAD and MNP) aims to accelerate recovery, reduce the intensity of symptoms, promote early restoration of function, prevent chronic pain and disability, improve health-related quality of life, reduce recurrences, and promote active participation of patients in their care (patients education) (Cotè et al., 2016, Haldeman et al., 2010).
Different recent papers confirmed that many commonly used methods for managing neck pain, including massage, cervical collar, transcutaneous electrical nerve stimulation, NSAIDs, short-wave diathermy, electrical muscle stimulators, showed no benefits when compared to placebo or added to another therapy (Wong et al., 2016, Sutton et al., 2016, Cotè et al., 2016).
A recent update, suggest that mobilization, manipulation, and clinical massage are effective for the management of neck pain, and found that electropuncture, strain-counterstrain, relaxation massage, and other passive physical modalities (heat, cold, diathermy, hydrotherapy, ultrasound) are not effective and should not be used in the management of neck pain (Wong et al., 2016).
As chronic neck pain may be associated with psychological complaints (e.g. anxiety, depression, fear avoidance behavior, catastrophizing), psychological help (e.g. cognitive-behavioral therapy) and patient education may be helpful (Blanpied et al., 2017).
The management of WAD is strongly dependant from the phase in which is the subject: in the acute phase advise encouraging return to usual activity and exercises is the best option (Meeus et al., 2012a), and immobilization (e.g. a soft collar) should be avoided. At the same time an early multidisciplinary intervention does not seem to be advantageous (Jull et al., 2013), and an early too intensive intervention may even reduce speed of recovery (Cotè et al., 2007).
However to nowdays it is not clear how to profile these subjects and differentiate them from those who require more multidisciplinary intervention (Cotè et al., 2007).
Differently, in the chronic phase a multidisciplinary intervention (including psychological intervention such as cognitive-behavioral therapy) seems to be necessary, but with no clear conclusion on the which is the best approach and the optimal combination (Pato et al., 2010).

A combination of exercises and cognitive-behavioral therapy seems to be effective for the management of chronic WAD, but the effect sizes for this multimodal program were quite small (Nijs et al., 2009, Seferiadis et al., 2004).
Other therapeutic procedure includes cervical epidurals (Benyamin et al., 2009), therapeutic medial branch blocks, and radiofrequency neurotomy (Manchikanti et al., 2009, Lord et al., 1996), pharmacological treatment (but with a lack of randomized controlled trials) (Wong et al., 2016), but these goes beyond the scope of this project so they have not been discussed.
MT is one of the most commonly used approach to manage neck pain, and may include manipulation, mobilization, neuromuscular therapies, and massage/soft tissue therapies (Basmajian and Nyberg, 1993); it will be discussed in detail in section number 5, as it represents the therapeutic protocol used in paper II .
However,a recent systematic review concluded that adding MT to exercise does not seem to improve outcomes in neck pain (Fredin and Lorås, 2017).
A recent systematic review added new evidence, concluding that structured education is cost-effective for WAD, whereas multimodal care including exercise and MT are cost-effective for neck pain (Velde et al., 2016).
Results on which is the best treatment are still conflicting, and this could explain why a huge variety of treatments for neck pain are offered in the everyday clinical practice.

3. TRIGGER POINTS (TrPs)

3.1 Definition, diagnosis and classification

A Myofascial Trigger Points (TrPs), is defined as a "hyperirritable spot within a taut band of a skeletal muscle that is painful on compression, stretching or contraction, and responds with a referred pain pattern distant from the spot" (Simons, 1999).
TrPs are often underdiagnosed by clinicians, not recognizing them as a source of pain, especially in musculoskeletal pain. They may be the primary dysfunction and not necessary a consequence of a medical condition or another cause (Mense and Gerwin, 2010).
TrPs are usually divided into active and latent TrPs: from a clinical viewpoint, active TrPs are those producing a pain familiar to the patient when stimulated, while latent produces pain as well, but that is not recognized as familiar by the subject (Simons, 1999).
Both active and latent TrPs may provoke muscle imbalance, motor dysfunction, altered agonist/antagonist relationship, and altered movement coordination (Lucas et al., 2004, Simons 1999, Ibarra et al., 2011).
Furthermore, although not responsible of spontaneous pain, latent TrPs provide nociceptive input to the dorsal horn (Xu et al., 2010).
The diagnosis of TrPs is usually clinically made with manual palpation, following the diagnostic criteria described by Simons (1999):

1) presence of a taut band in a skeletal muscle
2) presence of a tender spot within the taut band
3) reproduction of patient's spontaneous pain with sustained pressure (active TrPs)
4) presence of referred pain distant from the stimulated area
5) presence of a local twitch response (LTR) on snapping palpation

Although the present paper discusses the contribution of muscle triggers, such as TrPs, it should be emphasized that there is still a lack of diagnostic gold standard and a lack of recognized specific pathologies in the muscle tissue (Simons, 2004, Srbely et al., 2016).
In fact, the reliability of manual palpation has been criticized, with studies supporting a moderate to good reliability when the diagnostic criteria are followed (Sciotti et al., 2001, Gerwin et al.,1997, Walsh et al., 2016, Rozenfeld et al., 2017), and systematic reviews concluding that manual palpation is an unreliable tool for TrPs diagnosis, concluding that future investigation should focus on integration with

more reliable techniques (Myburgh et al., 2008, Lucas et al., 2009, Rathbone et al., 2017).
Other diagnostic tools (e.g. elastography, magnetic resonance elastography, ultrasound, vibration sonoelastography) have been studied to confirm the diagnosis of the TrPs, but they are not accessible in every-day clinical practice, so to nowdays the diagnosis remains manual palpation (Mariappan et al., 2010; Sikdar et al., 2009, Ballyins et al., 2011).
Referred pain seems to be the most reliable criteria for diagnosis with manual palpation, but doubts exist regarding the reliability of finding the tender spot within the taut band (Bron et al., 2007).
Referred pain occurs at the dorsal horn level, and it is the pain (or any other sensation) which is perceived at a remote site away from the location of the TrPs when stimulating it: central mechanisms must be part of the referred pain pathways, as it may be evoked in areas with full sensory loss (Laursen et al., 1999), and it can rapidly disappear with TrPs inactivation (Giamberardino et al., 2007).
An explanation for referred pain, comes from animal studies showing that sustained muscle damage (e.g. ischemia, overload) may sensitize dorsal horn neurons and open silent synapses in adjacent segments and excite neurons that supply the body regions in which the referred pain is felt (Hoheisel et al.,1994); furthermore muscle nociception promotes expanded and new receptive fields (Hoheisel et al.,1993) activating quiescent axonal connections between effective nerve fibers of dorsal horn neurons (Mense, 2010).
Referred pain may be evoked in few seconds with the stimulation of a TrPs, suggesting that neuroplastic changes which related to referred pain may be rapidly induced (Kuan et al., 2007).
Another important characteristic of TrPs is the LTR: it is a rapid, involuntary contraction within the muscle being stimulated, which can be elicited with snapping palpation perpendicular to the taut band, or with needle insertion (Chou et al., 2012). It is believed to originate from a spinal reflex, and it is related to the irritability of the TrPs, which directly related to the sensitization of muscle nociceptors (Hong and Simons, 1998, Rivner et al., 2001).
Its importance for achieving clinical improvements has been largely debated, but to date no firm conclusion can be drawn yet (Boyles et al., 2015, Kietrys et al., 2013, Perreault et al., 2017).
TrPs area shows a spontaneous electrical activity which can be detected with intramuscular needle electromyography when the muscle is at rest, and which is not present in normal muscle conditions (Hubbard et al., 1993, Simons et al., 2004); it originates from the extrafusal motor endplate, and represents involuntary focal muscle fiber contraction due to an abnormal spontaneous release of acetylcholine (ACh) (Ge et al., 2011).

Human experimental studies showed that the irritability of a TrPs was highly correlated with the amplitude of the spontaneous electrical activity, which is also associated with lowered PPTs (Kuan et al., 2007).
TrPs may be found in many painful conditions, such as tension-type headache (Fernández-de-las-Peñas et al., 2007b), migraine (Giamberardino et al., 2007), low back pain (Ramsook and Malanga, 2012), chronic pelvic pain (Jarrell et al., 2004,), lateral epicondylalgia (Fernández-Carnero et al., 2008), shoulder impingement (Hidalgo-Lozano et al., 2010), mechanical neck pain (Fernández-de-las-Peñas et al., 2007a), patellofemoral pain (Hains et al., 2010), temporomandibular disorders (Fernández-de-las-Peñas et al., 2010), knee osteoarthrosis (Itoh et al., 2008), and also in whiplash syndrome (Ettlin et al., 2008) and fibromyalgia (Ge et al., 2009).

3.2 Pathophysiology of TrPs

The exact mechanisms of TrPs development are not fully understood, but different factors, such as muscle overuse, repetitive minor muscle trauma/damage, psychological stress, or visceral disorders may be involved (Gerwin et al., 2004).
The integrated hypothesis is the most accepted theory for explaining the pathophysiology of TrPs: injured or overloaded muscle fibers could lead to involuntary shortening, loss of oxygen and blood supply, and increased metabolic demand on local tissue (Simons et al., 2004, Gerwin et al., 2004).
This model proposes an altered activity of the motor endplate, leading to an abnormal release of ACh, and to a sustained depolarization of post-junctional membrane of motor endplates. This would lead to sarcomere sustained contractions which may cause a local energy crisis due to the lack of oxygen, which is required together with glucose for the synthesis of adenosine triphosphate.
Furthermore, the lactic acid is not washed out into the bloodstream in sustained low-level contractions, leading to a decrease of pH of the area of the TrPs, which sensitize muscle nociceptors (Shah et al., 2005, Gautam et al., 2010).
In fact, this stimulates the release of a variety of endogenous substances, such as neuropeptides, arachidonic acid derivatives, substance P, calcitonin gene-related peptide, cytokines, prostaglandins, serotonin and bradykinin which may sensitize muscle nociceptors (Mense, 2001).
Once nociceptors are sensitized, they are more easily activated and may respond to normally innocuous stimuli, like light pressure: in addition to the nociceptor sensitization, non-nociceptors (the large diameter muscle afferents) are also sensitized at TrPs site, and are involved in pain generation (Ge et al., 2011, Li et al., 2009).

Shah demonstrated with microdialysis techniques, that the active TrPs biochemical milieu has significantly elevated levels of sensitizing substances (neuropeptides, arachidonic acid derivatives, substance P, calcitonin gene-related peptide, cytokines, prostaglandins, serotonin and bradykinin) compared with latent TrPs or healthy controls (Shah et al., 2005 and 2008).
However, the findings of Shah have so far not been replicated by any other studies, and the sample size of both his studies were very small.

3.3 TrPs in neck pain

In neck and shoulder muscles, TrPs often develops as a result of muscle overuse during low-intensity activities of daily living and sedentary works (e.g. office workers) (Treaster et al., 2006, Kaergaard et al., 2000). Prolonged computer work may provoke ischemia, leading to reduced blood flow, which may in turn sensitize nerve endings through the release of endogenous substances (Cagnie et al., 2012). It has been suggested that this may cause a decrease in intramuscular perfusion, leading to ischemia, hypoxia, insufficient adenosine triphosphate synthesis, Ca^{++} accumulation, and subsequent sarcomere contracture. This may lead to a vicious cycle that may have as final result the creation of TrPS in neck and shoulder muscles (Shah et al., 2015).
In both MNP and WAD subjects a number of active TrPs in neck and shoulder muscle greater than healthy subjects have previously been found (Ettlin et al., 2008, Fernández-de-las-Peñas et al., 2007a, Gerwin and Dommerholt, 1998), and both location and type of pain (i.e. tightening and burning) elicited by TrPs stimulation were similar to what usually felt by these subjects (Fernández-de-las-Peñas et al., 2007a, Ettlin et al., 2008).
A recent systematic review, concluded that TrPs are a prevalent clinical entity in patients with neck pain, with difference depending on the origin of neck pain (Lluch et al., 2015).
According to that, subjects with WAD and MNP in paper I were screened for the presence of active or latent TrPs in the suboccipital, upper trapezius, elevator scapula, temporalis, supraspinatus, infraspinatus and sternocleidomastoid muscle bilaterally, by an examinator blinded to subject's diagnosis.
The distribution of active TrPs between groups showed a significant difference ($P<0.001$), with WAD subjects presenting a mean of 6.71 active TrPs while the MNP had a mean of 3.26 active TrPs (**Table 3**). No statistically significant difference ($P=0.16$) was found for latent TrPs, and this could be expected as latent TrPs are normally found also in healthy subjects (Chaiamnuay et al., 1998, Fernández-de-las-Peñas et al., 2007a).

Table 3. Distribution of number of TrPs between WAD and MNP group (data from paper I)

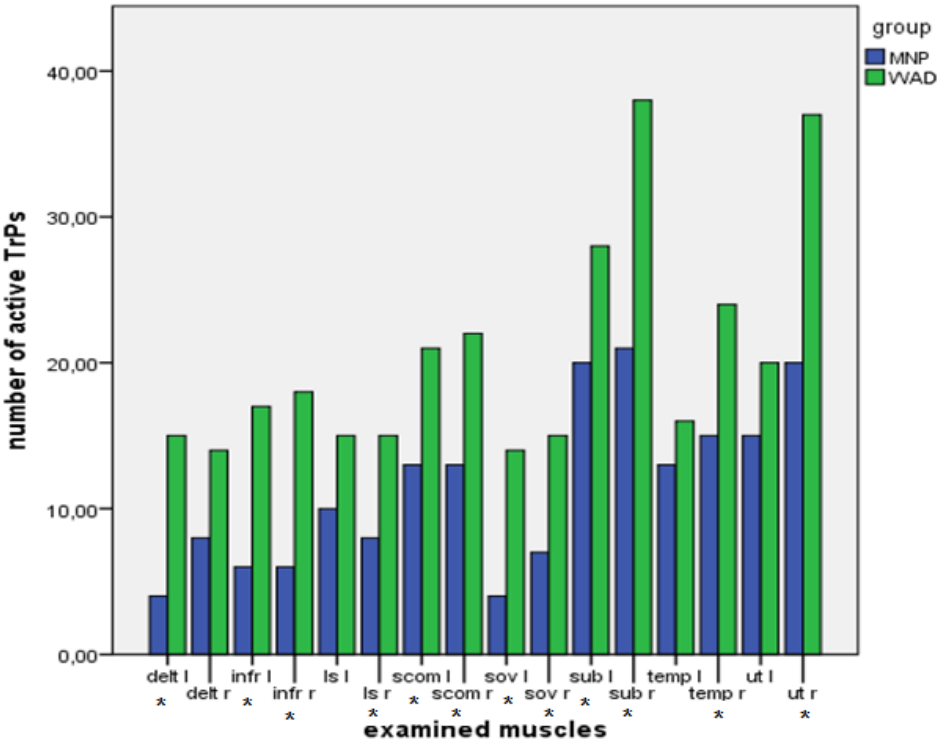
Table 3	WAD	MNP	P value
Active TrPs	6.71 ± 0.79	3.26 ± 0.33	**0.001***
Latent Trps	3.95 ± 0.57	2.82 ± 0.34	0.16

Data are expressed as mean ± standard deviation (95% confidence interval)

*Significant differences (P<0.05) between groups in paper I

Further, a higher prevalence of active TrPs in WAD has been found for all examined muscles, with significant differences in twelve muscles (all, P<0.04); in the remaining four muscles (left upper trapezius, left levator scapulae, left temporalis and right deltoid) WAD had a higher prevalence of active TrPs, but without a significant difference (all, P>0.07) (**Figure 3**).

Figure 3. Distribution of numbers of TrPs in the examined muscles in WAD and MNP subjects (data from paper I)



TrPs: trigger points; MNP: mechanical neck pain; WAD: whiplash-associated disorders; delt l: left deltoid; delt r: right deltoid; infr l: infraspinatus left; infr r: infraspinatus right; ls l: levator scapulae l; ls r: levator scapulae r; scom l: sternocleidomastoid left; scom r: sternocleidomastoid right; sov l: sovraspinatus left; sov r: sovraspinatus right; sub l: suboccipital left; sub r: suboccipital right; temp l: temporalis left; temp r: temporalis right; ut l: upper trapzius left; ut r: upper trapezius right

*Significant differences (P<0.05) between groups in paper I

A previous study has investigated the distribution of TrPs between WAD and MNP, finding a higher prevalence of TrPs in the semispinalis capitis in WAD, and no significant differences for trapezius pars descendens, levator scapulae, scalenus medius, sternocleidomastoideus, and masseter muscles (Ettlin et al., 2008).

Levator scapulae and sternocleidomastoid muscle were the only two muscles that were screened for the presence of TrPs in both paper I and the study performed by Ettlin et al. (2008), and the results may seem in contrast. But it is necessary to remember that Ettlin's study was performed on 124 whiplash patients and only 17 patients with non-traumatic chronic cervical syndrome, for these 17 patients inclusion criteria were not reported, and for the diagnosis of TrPs only 3 of 4 reported diagnostic criteria were needed.

In paper I, 49 WAD subjects and 56 MNP subjects were included, and for the diagnosis of active TrPs, the five criteria described by Simons (1999) were mandatory.

The differences in sample size and in the use of diagnostic criteria could explain the difference found between the two studies.

In paper I the only muscles in which TrPs diagnosis was performed without LTR reproduction were suboccipital muscles, as they can't be directly palpated. The diagnostic criteria were adapted for these muscles, as reported by Fernández-de-las-Peñas et al. (2006).

A recent systematic review and meta-analysis on the prevalence of TrPs in spinal disorders, concluded that active TrPs were present in all spinal pain disorders, and that no difference for latent TrPs between patients and healthy control was found (Chiarotto et al., 2016).

In this review, were included 12 studies on TrPs in spinal disorders, and paper I was one of the only two studies that has been ranked with high methodological quality.

Previous studies agreed on considering active TrPs important peripheral nociceptive input and possible initiators of CS, being related to lowered PPTs both locally (due to a sensitization of the TrPs area) and widespread (due to neuroplastic change) (Nystrom and Freeman, 2017, Freeman et al., 2009, Xu et al., 2010).

In fact, the presence of multiple TrPs (spatial summation), or the presence of TrPs for prolonged period (temporal summation) may sensitize spinal and supraspinal structures (Mense and Gerwin, 2010).

In paper I WAD subjects presented with more active TrPs in neck-shoulder muscles (spatial summation) compared to MNP subjects: however WAD subjects showed higher pain intensity and greater pain area, but without reaching statistically significant difference. This may partially be explained because we can't investigate from how long active TrPs are present, and thus MNP subjects may had TrPs from longer period (temporal summation), explaining why similar sensitization degree was found.

Further, also latent TrPs provide nociceptive input to the dorsal horn (Ge et al., 2011, Mense, 2010, Xu et al., 2010), and the distribution of latent TrPs was similar between the two groups.

In paper I, a correlation between the number of active TrPs and both pain intensity and pain area was found in the WAD group (both, P=0.03), but not in the MNP group.
These findings may support that the current subjective pain perception experienced may be modulated by active TrPs (which were more prevalent in WAD), supporting the idea that are they represents prolonged nociceptive inputs from the periphery, which may sensitize peripheral nociceptors first, and then central pathways (Herren-Gerber et al., 2004).
As pain levels were similar between the two groups, but the difference in active TrPs statistically significant (which are the TrPs producing spontaneous pain), other structures/mechanisms must play a role in pain intensity.
It may be possible that in MNP subjects other factors (e.g. poor posture, repetitive working task) were the main drivers of subjective pain perception, explaining why a direct correlation between symptoms (pain intensity and pain area) and the number of active TrPs was not found.
Furthermore, large variability between different subjects can be present, as reported by Nystrom and Freeman (2017) recently found that not all WAD subjects had a rapidly adjusting responses in PPTs after TrPs injections with local anesthetics, suggesting that also in WAD subjects TrPs role on modulation of widespread pressure pain hypersensitivity may be more relevant in specific sub-groups of WAD subjects than others.
Nevertheless, no significant differences for pain area and pain intensity were found in paper I between MNP and WAD subjects, indicating pain intensity and pain area are influenced also by other factors (e.g. psychological status, work related activity, health status, pain duration, other painful conditions).
In paper I a cause-effect relationship couldn't be established, as no treatment directed towards TrPs deactivation was applied to see if this related to an improvement of both clinical outcomes and PPTs.
In paper II, a part of the MT treatment protocol was directed towards TrPs deactivation: both WAD and MNP subjects showed a statistically significant improvement of neck pain intensity, neck-related disability, pain area extension (all, P<0.001) (**Figures 9,10,11**).
However, as the proposed approach included also other MT techniques, it's impossible to state a direct relationship between TrPs deactivation and outcomes improvement. Results will be discussed in section 5.3.
An interesting finding from papers III and IV, is that subjects presenting with active TrPs in upper trapezius muscle exhibited significant higher neck pain intensitiy, higher neck-related disability, and lower PPTs than those with only latent TrPs in the same muscle (all, P<0.01). This has been found in both MNP subjects, WAD

subjects, and in a mixed sample of 50% MNP and 50% WAD subjects (only PPTs were studied in the mixed sample of paper IV).

If active TrPs may be related to lowered PPTs, this can explain why WAD subjects which usually present with more active TrPs (according to paper I) have often higher signs of sensitization. This does not exclude the existence of MNP subjects with more active TrPs, which can promote higher sensitization.

These findings support the idea that active TrPs induces larger referred area and higher pain levels than latent TrPs (Hong et al., 1996), but to some degree also latent TrPs provide nociceptive input into dorsal horn neurons, and therefore they may contribute to the sensitization development (Ge et al., 2011, Mense, 2010, Xu et al., 2010).

Subjects presenting with active TrPs showed also greater pain area, but the difference was not statistically significant (found in both MNP and WAD subjects). Results are summarized in **Table 4**.

Table 4. Clinical and psychophysical outcomes depending on the presence of active or latent TrPs (data from paper III and paper IV)

Table 4	NPRS (0-10)*	NDI (%)*	Pain area (AU)	PPT upper trapezius (kPa)*	PPT tibialis anterior (kPa)*	PPT extensor carpi radialis longus (kPa)*
Mechanical Neck Pain, paper III						
Active TrPs	**3.9 ± 3.1 (2.9, 4.9)**	**25.6 ± 15.0 (20.7, 30.5)**	2173 ± 1839 (1547, 2799)	**259.2 ± 102 (202.1, 316.3)**	**398.2 ± 186.7 (319.4, 477.1)**	NA
Latent TrPs	**2.8 ± 2.5 (1.5, 4.2)**	**20.9 ± 10.5 (14.3, 27.6)**	1732 ± 1044 (890, 2575)	**372.3 ± 162.7 (295.4, 449.3)**	**491 ± 190.8 (384.8, 597.2)**	NA
Whiplash-associated Disorders, paper III						
Active TrPs	**4.5 ± 2.3 (3.5 ,5.4)**	**33.6 ± 14.6 (29.0, 38.3)**	2713 ± 1863 (2117, 3309)	**264.8 ± 151.7 (210.4, 319.2)**	**343.2 ± 157.5 (268.1, 418.3)**	NA
Latent TrPs	**2.5 ± 2.4 (1.2, 3.6)**	**22.4 ± 10.1 (16.3, 28.4)**	2468 ± 1603 (1695, 3241)	**343.5 ± 211.8 (272.9, 414.1)**	**475.1 ± 326.5 (377.7, 572.6)**	NA
Neck Pain, paper IV						
Active TrPs	NA	NA	NA	**202.9 ± 84.1 (178.2, 227.6)**	**313.6 ± 144.7 (271.1, 356.1)**	**185.2 ± 95.2 (157.3, 213.2)**
Latent TrPs	NA	NA	NA	**307.3 ± 87.7 (267.3, 347.2)**	**446.6 ± 158.6 (374.4, 518.8)**	**243.7 ± 74.5 (209.8, 277.6)**

TrPs: trigger points; NPRS: numeric pain rating scale; NDI: neck disability index; NA: not available, AU: arbitrary units, kPa: kilopascal

Data are expressed as mean ± standard deviation (95% confidence interval)

*Significant differences ($P<0.05$) between subjects with active or latent TrPs in paper III and IV

Nevertheless, the clinical relevance of this finding from paper III should be considered with caution at this stage since the differences between subjects with active and latent TrPs within the MNP group were relatively small and did not surpass the cut-off determined for pain (2 points), disability (7 points), and distant PPTs (97.9 kPa), while for local PPTs the cut-off of 47.2 kPa was reached (Chesterton et al., 2007, MacDermid et al., 2009, Schellingerhout et al., 2012, Walton et al., 2011).

The differences in the WAD group were higher and may be considered clinically relevant since they reached the cut-off established for pain, local PPTs, and distant PPTs.

However, the cut-off of 47.2 kPa for local PPT, and 97.9 for distant PPTs, were determined in acute neck pain subjects (Walton et al., 2011), while subjects from the present papers where chronic subjects, and the cut-off values may be a different.

It may be possible that a more detailed assessment of TrPs in more muscles would have revealed that subjects with multiple (and not only in upper trapezius) active TrPs, may show even greater signs of sensitization (due to spatial summation) compared to subjects with only latent TrPs in the same muscles.

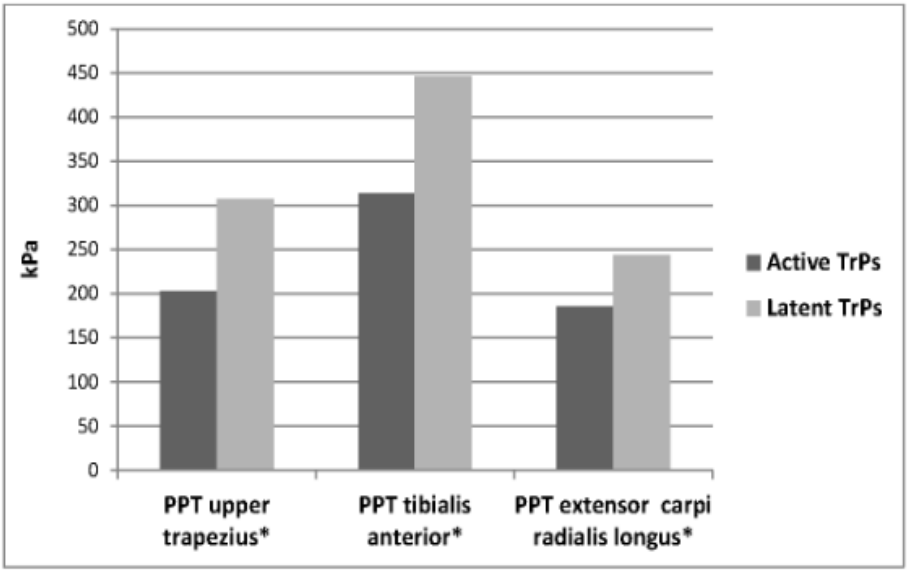
In paper IV, the differences in PPTs between subjects with active and latent TrPs in upper trapezius, reached the cut-off established for local PPTs (upper trapezius), and for PPTs in tibialis anterior, but not for extensor carpi radialis longus (Walton et al., 2011, MacDermid et al., 2009, Cleland et al., 2008) (**Figure 4**).

It is important to remember that also latent TrPs represent local nociceptive input (even if not symptomatic tender spots) which may to some extent send nociceptive informations to the dorsal horn (Ge et al., 2011), contributing to subjective (i.e. pain, neck-related disability, pain area) and psychophysical (i.e. PPTs) aspects of pain sensation.

The lack of a control group of healthy subjects without TrPs does not allow to fully understand the role of peripheral nociceptive input in the extent of pain sensation.

These results suggest that TrPs may contribute to the pain and disability experience, and to widespread pressure pain hypersensitivity in neck pain subjects.

Figure 4. The role of active and latent TrPs in upper trapezius muscle on PPTs levels (data from paper IV)



*Significant differences (P<0.05) between active and latent TrPs in upper trapezius muscle

kPa: kilopascal; PPT: pressure pain threshold

3.4 Treatment options

One important reason for treating TrPs, is that CS may be reverted (at least temporarily) in subjects presenting with TrPs with a proper management: in fact injections of active TrPs provoked a reduction of mechanical hyperalgesia, allodynia, and referred pain (Affaitati et al., 2011, Freeman et al., 2009, Giamberardino et al., 2007).
Several treatment modalities have been proposed for the management of TrPs: many of them are physical (manual) treatments involving the application of some form of They include ischemic compression (IC) (Cagnie et al., 2013), massage (Moraska et al., 2017), strain counterstrain (Ibanez-Garcia et al., 2009), spinal manipulation (Ruiz-Sáez et al., 2007), stretching (Kostopoulos et al., 2008), dry needling (Cagnie et al., 2015), muscle energy techniques (Nagrale et al., 2010), spray and stretch (Simons, 1999), integrated neuromuscular inhibition technique (Nagrale et al., 2010), transcutaeal electrical nerve stimulation (Rickards et al., 2006), US (Srbely et al., 2008), laser (Dundar et al., 2007).
Manual treatments are usually clinically effective for deactivating TrPs, and are the most commonly used in clinical practice: however most of the studies did not include a control group, so a placebo response can't be excluded.
Different invasive TrPs treatments including injection of local anesthetic, and botulinum toxin have been tried (Lavelle et al., 2007), but the general finding is lack of effect or convincing effect, with a lack of control conditions (Ho et al., 2007, Annaswamy et al., 2011).
Further, one of the most important treatment to prevent TrPs development and recurrence, is to eliminate/manage the cause (e.g. overuse, bad posture) which would lead to their recurrence, and patient education (Hanten et al., 2000, Lartigue et al., 2009).
There is in increasing interest in both clinical and research setting on dry needling, but the effectiveness of manual treatment should not be overlooked as it seems to produce the same results in both the short and the long term (Rayegani et al., 2014, Cagnie et al., 2015, de Meulemeester et al., 2017).
According to the TrPs treatments literature, in paper II, part of the MT treatment was directed to TrPs deactivation using IC, as it is the most frequently used technique for treating TrPs and it has shown good results (Cagnie et al., 2013, Aguilera et al., 2009, Hains et al., 2010, Moraska et al., 2013).
IC was applied to TrPs in the suboccipital, upper trapezius, levator scapulae, and sternocleidomastoid muscles bilaterally.
During the procedure, the applied force provoked a small to moderate discomfort, and the pressure was sustained for each muscle until subjects reported a decrease of

pain of around 50%, in any case never less than one minute and never more than two minutes.
The results will be presented in section 5.3, as TrPs deactivation was just a part of a MT standardized protocol including also joint treatment and specific exercises, as TrPs treatment seems to be more effective when integrated with a multimodal approach (Renan-Ordine et al., 2011, Bron et al., 2011)

4. SENSITIZATION

4.1 Central sensitization (CS)

CS is defined as an "increased sensitivity of cortical and spinal neurons to sensory stimuli (Woolf, 2011). It may include an increased activity of pain facilitation pathways, malfunctioning of descending pain inhibitory pathways (Meeus et al., 2008), which may also be the cause of a dysfunctional endogenous analgesic control in humans.
Furthermore, CS may include also an altered sensory process in the brain, temporal summation (Wind-up) (Staud et al., 2007), and increased activity of pain facilitatory mechanisms (Meeus and Nijs, 2007).
Clinically, CS is typically characterized by disproportionate pain and disability in relation to the nature and extent of injury or pathology: this differs from nociceptive pain, where the severity of pain is related to the nature and extent of tissue injury or pathology (Nijs et al., 2014).
In fact, CS may result in an increased sensibility to various stimuli: chemical, temperature, electrical, stress, emotions, mental load, light, noise/sound, weather, food, and they can all be considered manifestation of the hyper-responsiveness of the CNS (Desmeules et al., 2004, Kasch et al., 2005, Meeus et al., 2008, Banic et al., 2004).
Finally, maladaptative psychosocial factors (e.g. negative emotions, poor self-efficacy, maladaptive beliefs and pain behaviors) are often present in CS patients (Smart et al., 2012).
Clinical and experimental characteristics of CS have been observed in various chronic pain conditions (Drewes et al., 2006, Fingleton et al., 2015, Julien et al., 2005, Nijs et al., 2014), but not all chronic pain patients show CS features: it is mandatory to recognize that specific sub-groups of patients with chronic pain conditions may present with CS at different degrees (Fernández-de-las-Peñas et al., 2017, Arendt-Nielsen et al., 2015).
It is still unknown why some people are more prone to develop CS, but it seems that genetic predisposition and other biopsychosocial factor could play a role (Descalzi et al., 2015, Mourão et al., 2010).
CS could also be present during acute pain conditions, like early whiplash patients, where abnormal sensory processing have been found to develop in the first week after the trauma, and, once established, it has an important predictive ability for the development of chronic pain (Sterling et al., 2003a).

Pain sensitization may be present at different degrees, and the longer the pain or pathology persists, the more likely CS becomes dominant in the clinical picture (Arendt-Nielsen et al., 2015); however it has been experimentally rapidly induced in healthy subjects, with a sustained nociceptive peripheral input (Xu et al., 2010).
Signs of CS have been found in different medical conditions (e.g. diabetes, chronic pancreatitis, peripheral arterial disease, sickle cell anemia, rheumatoid arthritis, hypertension, chronic cough, bone cancer, fibromyalgia, irritable bowel syndrome, dysmenorrhea, suggesting a possibly greater excitability of the CNS of these subjects (Woodcock et al., 2010, Vaughan et al., 2015, Meeus et al., 2007, Verne et al., 2002, Moshiree et al., 2006, Meeus et al., 2012b, Griggs et al., 2016, Arendt-Nielsen et al., 2014, Xue et al., 2012, Lang et al., 2006).
Further, signs of CS have also been found in several musculoskeletal pain conditions, such as knee pain (Arendt-Nielsen et al., 2010), epicondylalgia (Fernández-Carnero et al., 2009), carpal tunnel (Fernández-de-Las-Peñas et al., 2009), shoulder pain (Coronado et al., 2014), temporo-mandibular disorders (La Touche et al., 2017), tension-type headache (Ashina et al., 2006), low back pain (O'Neill et al., 2007).
Clinicians must be aware of the possibility of CS as it could make more difficult the clinical reasoning process (Nijs et al., 2011), and potentially limiting the rehabilitation outcome (Jull et al., 2007a).
Finally, it is important to remember that CS is a wording derived from the animal neuro-physiological literature, while in humans CS has been studied mainly with clinical observation, and experimental pain research may bridge the gap between animal studies and clinical observation in humans.

4.2 Assessment of sensitization

Central manifestations may be difficult to quantify with standard clinical examination, but QST may be helpful in the measurement of CS: specific tools have been proposed to analyze different aspects of CS, such as temporal summation (wind-up), after sensation, spatial summation, reflex receptive fields, descending pain modulation, offset analgesia, referred pain areas (Arendt-Nielsen and Yarnitsky, 2009).
Not all the QST may be easily applied in the clinical setting, and a variety of diagnostic surrogate markers, besides clinical history (e.g. intensity, character/modality, spatial and temporal characteristics, spontaneous/provoked, and possible exacerbating factors of the pain), are being used for assessment including questionnaires (e.g. neuropathic pain scales and pain features), simple bedside QST,

and mapping of areas with sensory abnormalities (Arendt-Nielsen and Yarnitsky, 2009).

A lot of scientific papers refers to diagnosis, clinical findings, and treatment of CS, but it is necessary to remember that to nowdays it has never been directly measured in humans, and the only possible measurement of its clinical manifestations (i.e. hyperlagesia and allodynia) is through proxies. The terminology itself is commonly used improperly, as according to IASP definition, the word CS should only be applied when both input and output of the neural system under study are known (e.g., by controlling the stimulus and measuring the neural event) (Merskey and Bogduk, 1994).

Further, the fundamental question is if sensitization at all can be reliably and quantitatively assessed. Direct electrophysiological recordings from peripheral nociceptive afferents are not clinically applicable and recordings from central neurons are not an option for assessing sensitization in humans.

As central manifestations can't be measured directly in humans, experimental pain testing (i.e. QST) are commonly used as a proxy for measuring hyperexcitability of the central nervous system (Arendt-Nielsen and Yarnitsky, 2009, Curatolo et al., 2011b).

It is important for clinicians to be able to identify CS in patients, for an early assessment, as they may require a different therapeutic approach (Curatolo et al., 2006, Nijs et al., 2011).

Unfortunately, no gold standard for diagnosing CS exists: two questionnaires have been developed (i.e. Pain Sensitivity Questionnaire, Central Sensitization Inventory), but it seems that clinical and physical assessment is necessary in order to identify more reliably CS patients (Nijs et al., 2014).

From a clinical view-point, guidelines for the recognition of CS in patients with musculoskeletal pain have been proposed, but not validated, and they are of limited help to the clinicians in the decision-making process (Curatolo et al., 2001, Banic et al., 2004), and remains unclear how clinicians can recognize CS in individuals patients.

The clinical assessment and listen to the story of the patient, can give clues that will help the clinician in the recognition of CS (subjects show a general intolerance to any kind of physical or emotional stressors).

Symptoms like fatigue, concentration difficulties, not-refreshing sleep, sleep disturbances in general, are frequently experienced by CS patients (Yunus et al., 2007).

The presence of prior pain conditions may increase the probability of developing CS (Carstensen et al., 2008), information about abnormal disease course and the general medical conditions (Nijs et al., 2010) may be also helpful for the clinicians.

Informations about the general health status was collected in paper IV, and it's relationship with sensitization was studied: the results are reported in section 4.4.
An easy and quick QST that can be used in clinical practice, is the assessment of PPTs using a pressure algometer both in the painful and in pain-free distant area. The registered values should be significant lower from the values found in healthy subjects, to suppose the presence of CS mechanisms.
The amount of force and stress applied with the pressure algometer, has previously found to distributed more in the superficial versus the deep muscles (Finocchietti et al., 2011a), and is influenced by thickness of adipose tissue, potentially limitating the interpretation of algometry findings (Finocchietti et al., 2011b).
For that reason, in the present project PPTs were assessed in different superficial muscles (i.e. upper trapezius, tibialis anterior, extensor carpi radialis longus): the mean PPTs values of the subjects included in paper II, III, and IV (see **Table 2**) were lower than PPTs reported in healthy subjects studies (Rolke et al., 2006, Waller et al., 2015, Antonaci et al., 1998).
However, there is still a lack of reference standard that may indicate when the PPTs values are indicating the presence of CS.
Useful informations may be obtained assessing the psychophysical response after exposure to experimental painful stimuli in both patients and healthy subjects, as alterations in the response may help in detecting subjects with CS processes (Coronado et al., 2014), but these assessment may be performed only experimentally and are not helpful for clinicians.
Other manifestations of CS may be assessed in experimental studies, and include also other measurement, as nociceptive withdrawal reflexes, reflex receptive fields, thermal pain thresholds, wind-up of C fibers, brachial plexus provocation test and pinprick stimuli, which can all be proxies for the level of CS, but they goes beyond the scope of this paper so will not be discussed more deeply (Rolke et al., 2006).
Finally, clinicians should always remember that CS is not an all-or-nothing phenomenon, but it can be present at different degrees in patients with the same medical diagnosis, but different clinical manifestations (e.g. whiplash associated disorders, non-specific low back pain) (Roussel et al., 2013).
For example, as previously discussed, CS has been found to develop very soon in whiplash patients (Sterling et al., 2003a and 2006), but not all acute whiplash patients present signs of CS.
It is clearly emerging the need of sub-grouping subjects with various musculoskeletal pain conditions, distinguishing between subjects in which CS manifestations dominate the whole picture, from those who have a clinical presentation without (or with low) signs of CS.

4.3 The role of TrPs in driving sensitization

The presence of multiple or long lasting TrPs may sensitize supraspinal centers (Mense and Gerwin, 2010), resulting in enhanced descending facilitation that contributes to the amplification and spreading of pain (Nystrom and Freeman, 2017, Graven-Nielsen, 2006).
It has been experimentally shown, that the mechanical stimulation of a latent TrPs, induced mechanical hyperalgesia in extrasegmental deep tissue (Xu et al., 2010).
Furthermore, in experimental pain studies, inactivation of active TrPs with anesthetic injections significantly decreased mechanical hyperalgesia, allodynia, and referred pain, which are all manifestations of CS (Freeman et al., 2009, Affaitati et al., 2011, Giamberardino et al., 2007): it is important to remember that CS is a reversible process which can be modulated by TrPs to some extent.
Thus, TrPs are considered a peripheral nociceptive input, which may produce and contribute to CS (Freeman et al., 2009), but on the other hand, CS may increase the TrPs sensitivity through segmental pathways, resulting in decreased PPTs over TrPs, and increased amplitude of the spontaneous electrical activity (Srbely et al., 2010).
Furthermore, TrPs are one of the major contributors to the impaired descending inhibition in chronic musculoskeletal pain conditions, leading to an increased mechanical pain sensitivity of muscle tissue itself (Graven-Nielsen, 2006).
In both paper III and IV, it was found that subjects with active TrPs in upper trapezius muscle exhibited lower PPTs (both locally and in pain-free distant area) than those with latent TrPs in the same muscle (**Table 4**).
This has been found in both WAD and MNP subjects (Paper III), and in a mixed sample of WAD and MNP subjects (Paper IV), supporting the importance of active TrPs on widespread pressure pain hypersensitivity, regardless the origin of neck pain.
Further, it has been previously experimentally reported a pain model where TrPs have been proposed as at the basis for sensitization in tension-type headache (Fernández-de-las-Peñas et al., 2007c).
These findings support the importance of active TrPs on CS manifestations in neck pain subjects regardless the pathogenesis of neck pain complaints.
In paper I it has been found that WAD subjects present a greater number of active TrPs in neck and shoulder muscles compared to MNP (**Figure 3 and Table 3**): this could be one of the factors contributing to the higher degree of CS usually found in WAD subjects. Nevertheless, no significant differences for pain area and pain intensity were found in paper I between MNP and WAD subjects, indicating pain intensity and pain area are influenced also by other factors (e.g. psychological status, work related activity, health status, pain duration).

As CS is a progressive phenomenon, and TrPs may develop in both neck pain populations, it seems that identify sub-group of MNP subjects with high level of CS may be possible, as previously reported (Javanshir et al., 2010, Johnston et al., 2008a, Mejuto-Vasquez et al., 2014, Lopez-de-Uralde-Villanueva et al., 2016). Recently, four cluster of neck pain patients (mixed sample including also whiplash subjects) subjects have been identified according to level of PPTs locally and in pain-free distant location: the most common cluster (67% of the total sample) included neck pain subjects presenting with signs of central pain processing dysfunction (Walton et al., 2017).
From a clinical viewpoint, there is the need to translate group findings to individual subjects, in order to be helpful in terms of prognosis and individually tailored treatment choice, as the mean degree of CS is not representing all subjects from a sample (Walton et al., 2017).

4.4 Health history and CS

Collecting data about the general health status of the subject might help the clinicians with useful information in relation to the degree of CS (Nijs et al., 2010), as previous pain conditions may increase the probability of poor outcome and persistent pain (possibly related to CS) (Carstensen et al., 2008).
Indeed, signs of CS have been found in many medical conditions and musculoskeletal pain conditions (O'Neill et al., 2007, Ashina et al., 2006, Bouwense et al., 2013, Griggs et al., 2016).
History of prolonged medication intake may add useful information as long terms intake of some medications (e.g. analgesic overuse) may promote a generalized hyperalgesia (Angst et al., 2006, Lee et al., 2011, Ferrari et al., 2015).
In paper IV, the use of analgesics daily or almost daily for more than 1 month during the last 12 months was defined as long terms intake of medication, which is a common situation in neck pain subjects (Zwart et al., 2004).
One of the most studied relationship between medication overuse and CS is medication overuse headache, in which altered pain perception has been found, and which has found to improve after detoxification (Munksgaard et al., 2013, Evers et al., 2010).
Furthermore, in paper IV medication taken on a regular basis for specific medical conditions were also considered for long terms intake of medication, as their interaction with CS have not been previously studied.
Medication which are commonly used in the management of CS manifestations (e.g. pregabalin, gabapentin, antidepressant, N-Methyl-D-aspartate antagonists, sodium

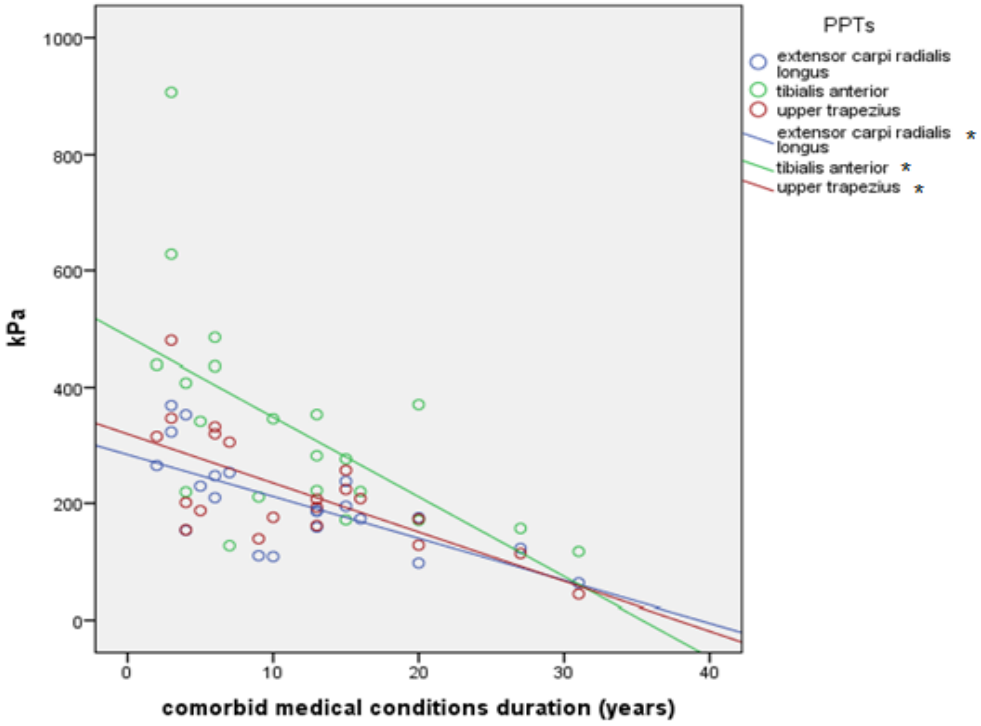
channel blockers, NSAIDs) were not considered in the analysis of medication (Curatolo et al., 2006, Nekovarova et al., 2014, Sawynok et al., 2001).
For example, the antinociceptive effect of paracetamol is known, but conversely, the chronic use of paracetamol may result in the loss of analgesic efficacy and, in its more extreme form, may produce analgesic-related painful conditions (Srikiatkhachorn et al., 2000).
This support the idea that prolonged medication intake may to some extent have an influence on CS progression.
Persistent postoperative pain may develop in 10% to 50% of individuals after common operations (Kehlet et al., 2006): many common surgeries may be associated with the development of CS (Juhl et al., 2008, Fernández -Lao et al., 2011, Sanchez-Jimenez et al., 2014, Skou et al., 2013, Mi-Hyun Kim et al., 2014).
Surgery, by nature, involves the cutting of tissues (e.g. nerves, skin, deeper tissues) leading to an inflammatory response, which in some people may over time lead to the development of deep tissue hyperalgesia (Kehlet et al., 2006).
In particular, the activation of deep tissue nociceptors has been shown to induce more and longer central nervous nociceptive activity than the activation of cutaneous fibers (Wall and Woolf, 1984).
On the other hand, it has been reported a normalization of widespread pressure pain hypersensitivity after total hip replacement, suggesting that in some subjects removing the peripheral input may be the most important factor (Aranda-Villalobos et al., 2013, Graven-Nielsen et al., 2012) for reducing CS manifestations.
To the authors knowledge, a general investigation of the role of health history (i.e. comorbid medical conditions, prolonged medication intake, comorbid musculoskeletal pain conditions, previous surgical operations) on sensitization in neck pain subjects have never been studied before.
The hypothesis was that subjects with longer and worse health history outcomes, would show greater signs of CS.
In paper IV, a mixed sample of neck pain subjects (50% MNP and 50% WAD) were assessed for PPTs over upper trapezius, extensor carpi radialis longus and tibialis anterior muscles, for the presence of active/latent TrPs over upper trapezius muscles, and for health history. In paper IV, differently from the other papers, subjects with WAD and MNP were grouped together for the statistical analysis, creating a mixed sample of neck pain subjects.
Two aspects of each health history variables were studied: the number of the condition for each variable, and the duration (or time) for each variable.
In subjects presenting with more than one condition for any variable, in the analysis on duration (or time) the oldest condition was considered. By doing so, it has been possible to study the relationship of the health complaints with the longest duration and CS. For comorbid medical conditions it was registered since how many years

subjects suffers from the oldest of them, for prolonged medication intake it was registered when did they start taking the medication they are taking from longer time, for other musculoskeletal pain conditions it was registered when did they start to suffer from the oldest musculoskeletal pain they have, and for surgical operations it was registered the time passed since the oldest operation they had.
Significant strong to moderate negative correlations between the duration of health history variables and PPTs were found:

- between the duration of comorbid medical condition and: PPT over upper trapezius (r_s=-0.61; P<0.001), PPT over extensor carpi radialis longus (r_s=-0.7; P<0.001), and PPT over tibialis anterior (r_s=-0.67; P<0.001) muscles
- between the duration of prolonged medication intake and: PPT over upper trapezius (r_s=-0.75; P<0.001), PPT over extensor carpi radialis longus (r_s=-0.66; P=0.01), and PPT over tibialis anterior (r_s=-0.62; P=0.02) muscles
- between the duration of other musculoskeletal pain condition and: PPT over upper trapezius (r_s=-0.65; P<0.001), PPT over extensor carpi radialis longus (r_s=-0.79; P=0.001), and PPT over tibialis anterior (r_s=-0.52; P=0.03) muscles
- between the time passed since previous surgical operation and: PPT over upper trapezius (r_s=-0.55; P<0.001), PPT over extensor carpi radialis longus (r_s=-0.45; P=0.04), and PPT over tibialis anterior (r_s=-0.47; P=0.03) muscles.

The longer subjects have been suffering from a comorbid medical condition, the longer they have been exposed to prolonged medication intake, the more time has passed since a surgical operation, and the longer they have been suffering from other musculoskeletal pain conditions, the lower were the PPTs both locally and widespread (**Figures 5,6,7,8**).These findings support the role of time in the development and progression of pain hypersensitivity, as also found in a previous study in which an association between pain duration and PPT levels was found (Arendt-Nielsen et al., 2015).
Similar findings have recently been found in tension-type headache: subjects with a longer history of pain exhibited higher widespread pressure pain hypersensitivity (Fernández -de-Las- Peñas et al., 2017).

Figure 5. Scatter plot of correlation between the duration of comorbid medical conditions and PPTs over upper trapezius, extensor carpi radialis longus, and tibialis anterior muscles (data from paper IV)



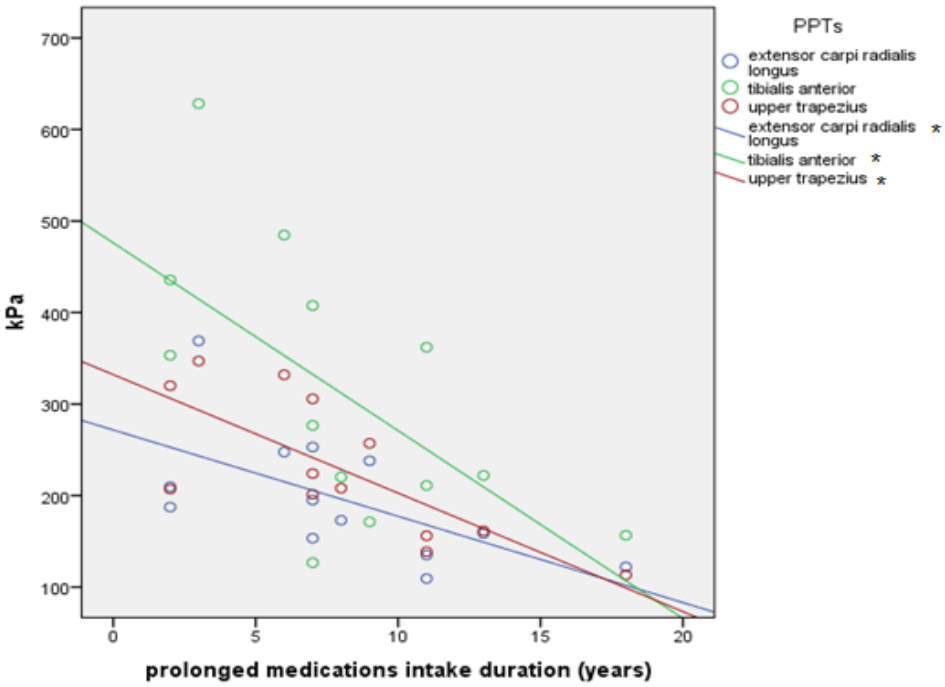
kPa: kilopascal; PPTs: pressure pain thresholds. Note that some points are overlapping. A negative linear regression line is fitted to the data

*Correlation is significant at the 0.01 level (2-tailed)

These findings may suggest that the long-lasting nociceptive input (comorbid medical conditions and other musculoskeletal pain conditions) or nociception from a tissue injury (as a result of previous surgical operation) may promote further development of widespread hyperalgesia during time.
The duration of the period taking continuous medication may be related to a specific medical condition for which the subjects are taking medication (remanding to the time suffering from a medical condition), or self-management of various symptoms

with analgesic drugs abuse which may promote hyperalgesia (Srikiatkhachorn et al., 2000).
Nevertheless, no longitudinal studies have been performed to nowdays, and they are needed to further investigate the transition from acute and localized pain conditions to a widespread pressure pain hypersensitivity.

Figure 6. Scatter plot of correlation between the duration of prolonged medications intake and PPTs over upper trapezius, extensor carpi radialis longus, and tibialis anterior muscles (data from paper IV)

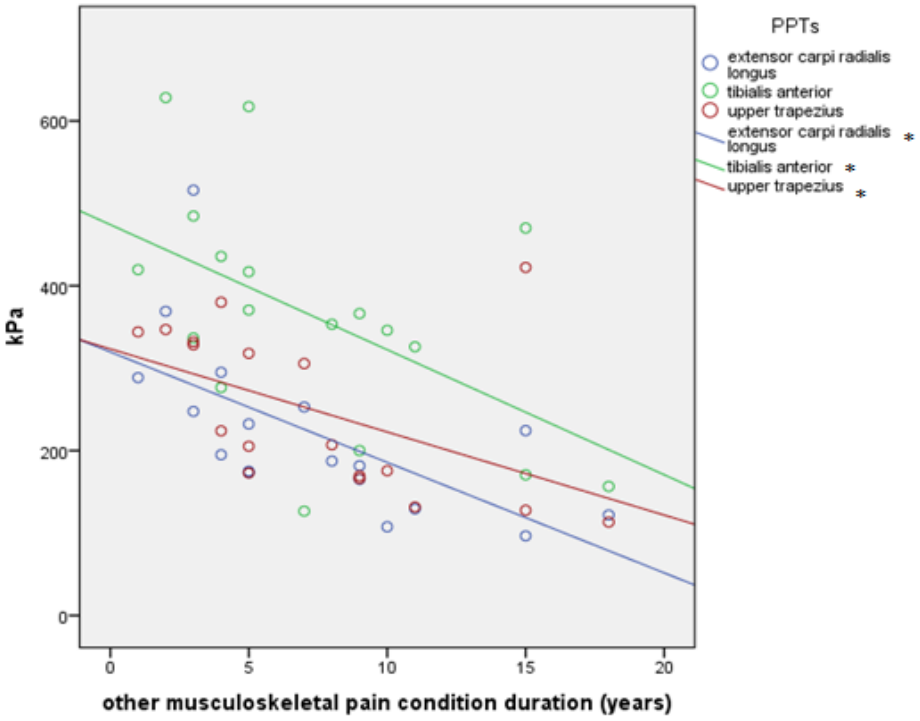


kPa: kilopascal; PPTs: pressure pain thresholds. Note that some points are overlapping. A negative linear regression line is fitted to the data

*Correlation is significant at the 0.01 level (2-tailed)

The importance of time in the transition from localized pain to a widespread pain condition, has been suggested by Graven-Nielsen and Arendt-Nielsen: tissue injury and nociception from deep tissue (e.g. TrPs) causes a progressive sensitization of the pain system along the neuroaxis to the CNS centers. When a larger part of the central pain system is sensitized, widespread pressure pain hypersensitivity will develop. The time necessary to this progressive sensitization is still unclear (Arendt-Nielsen et al., 2015, Fernández-de-las-Peñas et al., 2017, Graven-Nielsen and Arendt-Nielsen 2010).

Figure 7. Scatter plot of correlation between the duration of other musculoskeletal pain conditions and PPTs over upper trapezius, extensor carpi radialis longus, and tibialis anterior muscles (data from paper IV)

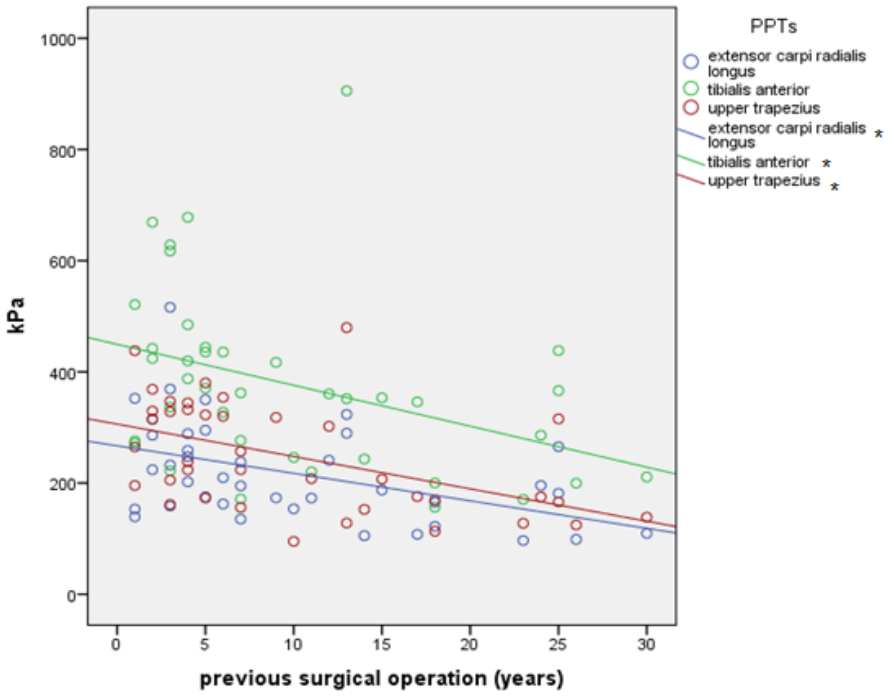


kPa: kilopascal; PPTs: pressure pain thresholds. Note that some points are overlapping. A negative linear regression line is fitted to the data

*Correlation is significant at the 0.01 level (2-tailed)

According to that, the duration of health status variables may promote a progressive sensitization, explaining why in paper IV the duration of health history complaints was related with widespread pressure pain hypersensitivity.
The lack of a healthy control group does not allow to generalize the findings of paper IV, as these correlations may be present also in other conditions or healthy subjects.
As paper IV was an explorative study and the study sample was to small, separate analysis for every different type of medical condition, musculoskeletal pain conditions, medication intake, surgical operation were not performed.
No associations between the number of health history variables and PPTs were found (all, $P>0.15$). A possible explanation for that could be that the mean number of comorbid medical conditions (0.5), regular medication intake (0.3), surgical operations (1.3), and comorbid musculoskeletal pain conditions (0.45) found in our sample was low.
Future research should focus on longitudinal studies, which would help in better understanding the spreading of pressure pain hypersensitivity over time.

Figure 8. Scatter plot of correlation between the time passed from receiving surgical operations and PPTs over upper trapezius, extensor carpi radialis longus, and tibialis anterior muscles (data from paper IV)



kPa: kilopascal; PPTs: pressure pain thresholds. Note that some points are overlapping. A negative linear regression line is fitted to the data

*Correlation is significant at the 0.01 level (2-tailed)

4.5 Management of CS

When CS may dominate the clinical picture of the patient, this could limit the response to treatment (Jull et al., 2007a), as removing or reducing the peripheral input may not be sufficient, and a multimodal approach is necessary, involving

pharmacological aspects , cognitive information-process approaches and rehabilitation treatments (Nijs et al., 2011).
The following approaches may be needed: 1) target the periphery removing the peripheral nociceptive input (when possible), 2) specific pharmacologic intervention acting at supraspinal and spinal level, 3) psychologic intervention, 4) exercise and education (for increasing the activation of descending inhibitory systems) (Curatolo et al., 2006, Nijs et al., 2011).
The main target can be the brain (top-down approach), or the peripheral input (bottom-up): the primary target should depend on the clinical picture, as some subjects may present with a clear evidence of peripheral nociceptive input (e.g. TrPs or osteoarthritis), and some may not (Nijs et al., 2014).
For example, in some chronic WAD subjects cervical radiofrequency neurotomy may reduce CS, but in this study a placebo group was missing (Smith et al., 2014).
Further, inactivation of active TrPs, may provoke a segmental and generalized desensitization effect, supporting the importance of modulating CS through the periphery (Xu et al., 2010, Herren-Gerber et al., 2004).
Surgical operation aiming at reducing the nociceptive input from the damaged tissue, has shown to decrease the degree of CS in some patients with hip degeneration (Aranda-Villalobos et al., 2013, Graven-Nielsen et al., 2012).
At the same time, sustained nociceptive stimulation (activation) of latent TrPs in healthy subjects may initiate widespread CS, confirming that TrPs may be an important peripheral pain generators that may rapidly initiate CS (Xu et al., 2010).
MT can be considered helpful in reducing the peripheral nociceptive input (thus leading to less barrage to the CNS), but on the other hand may be a stressor as well producing more nociceptive input. In fact, too strong techniques or exercises may accelerate CS (Nijs et al., 2009) instead of being helpful, so they should be dosed according to the response of the patient. This would be indicating that the descending anti-nociceptive pathways are unable to suppress temporal summation (wind-up) of nociceptive stimuli from the periphery.
In paper II the proposed treatment protocol was aiming at reducing the peripheral nociceptive input, using MT and specific neck exercises (increasing the activation of descending inhibitory systems).
Both WAD and MNP subjects showed a significant decrease of neck pain intensity, neck-related disability, pain area extension (all, $P<0.001$) (**Figure 9,10,11**), but not a significant increase (hypoalgesia) in PPTs (all, $P>0.222$).
These findings seem to indicate that even if symptoms reported by subjects improves, widespread pressure pain hypersensitivity may not significantly change. This may be due to the limited protocol we used: targeting the periphery with may be necessary as the peripheral input seems to be important for maintaining the CS (Baron et al., 2013), but not sufficient for all neck pain subjects, as probably more

sensitized subjects need a multimodal approach (i.e. pharmacological or psychological), also targeting the CNS directly (Nijs et al., 2011).
This was found in both groups, suggesting that also some MNP subjects may need a multimodal approach not limitated to MT and exercises in order to improve signs of CS.
In fact, being the brain CNS sensitized, it should be also targeted of the treatment, and biopsychosocial approach, patients education, pharmacological interventions (e.g. pregabalin, gabapentin, tricyclic antidepressant, N-Methyl-D-aspartate antagonists, sodium channel blockers) may all be helpful intervents (Curatolo et al., 2006, Nekovarova et al., 2014, Sawynok et al., 2001): the main goal is to activate inhibitory descending system and desensitize the CNS (Nijs et al., 2014).
The pharmacological management of CS was out of the scope of this thesis, in which the proposed therapeutic protocol was composed by MT and exercises, and will not be discuss in details.

5. MANUAL THERAPY (MT)

5.1 MT in musculoskeletal pain conditions

MT is a combination of techniques (as manipulation, mobilization, and soft tissue therapies, among others) and movement applied by experienced clinicians than may target (directly or indirectly) a variety of anatomical structures (i.e. muscles, joints, nerves, ligaments, tendons, disc), with the intent to improve the pain experience of the patients, and to restore the normal biomechanical function (Basmajian and Nyberg, 1993).
Mobilization is described as a low-grade passive movement (within its passive and active range of motion (ROM)) with varying amplitudes (Pool et al., 2006), in contrast to manipulation, a high-velocity, low-amplitude thrust technique in which manual force is applied to joints beyond its active and passive ROM (McReynolds and Sheridan, 2005).
Different papers suggest MT as effective (but often lacking of a control group) in the management of musculoskeletal disorders, including shoulder pain, hip osteoarthritis, knee osteoarthritis, carpal tunnel syndrome, low back pain, tension-type headache, cervicogenic headache, and neck pain (Chaibi and Russel 2012, Bialosky et al.,2009, Espí-López et al., 2014).
Further, It is rarely associated with serious complications (less than most medications) (Carnes et al., 2010).
A recent systematic review, concluded that moderate evidence exists supporting that MT reduces widespread pressure pain hypersensitivity in musculoskeletal pain, but the clinical relevance remains still unclear (Voogt et al., 2015). This could seem in contrast with the findings of paper II, but it is necessary to remember that in the review of Voogt et al (2015) all musculoskeletal pain were analyzed, while considering only neck pain studies, they also found inconsistent conclusions, with two studies finding significant results, and two studies finding no significant results.

5.2 Mechanisms of action of MT

MT is likely to be effective through both biomechanical and neuro-physiological mechanisms (Bialosky et al., 2009), but the mechanisms are not fully understood to date.

These two aspects interact as biomechanical parameters (i.e. force, duration, direction of a technique) produces dose-dependent neuro-physiological responses (e.g. EMG activity, muscle inhibition, hypoalgesic responses) (McLean et al.,2002, Colloca et al., 2006).
Biomechanical effects have shown only a transient effect (Hsieh et al., 2002), poor reliability of assessment (Seffinger et al., 2004), and poor specificity of action on the targeted segment (Herzog et al., 2001, Ross et al., 2004): in fact, improvement in signs and symptoms is obtained also targeting an area away from symptoms location (Cleland et al., 2007, Vicenzino et al., 1996).
These information about biomechanical effects suggests that additional mechanisms of action may be relevant: however, the cascade of neuro-physiological responses is initiated by a mechanical force from the periphery (Bialosky et al., 2009).
Neuro-physiological mechanisms includes peripheral, spinal, and supraspinal mechanisms.
Peripheral mechanisms may include a significant reduction of blood and serum cytokines levels (Teodorczyk-Injeyan et al., 2006), and an increase of blood levels of beta-endorphin, anandamine, N-palmitoylethanolamide, serotonin and endogenous cannabinoids (McPartland et al., 2005).
MT may modulate spinal mechanisms as well, with an animal study showing decreased activation of the dorsal horn after intervention (Malisza et al., 2003a), hypoalgesia (Vicenzino et al., 2001), changes in muscle activity (Herzog et al., 1999), and decrease of temporal summation (Bishop et al., 2011).
The involvement of supraspinal systems has been corroborated through the observation of hypoalgesia and excitation of the sympathetic nervous system (e.g. changes in heart rate, blood pressure, skin blood flow) with the application of MT techniques (Kingston et al., 2014), and an MRI study on brain region involved in pain experience, which showed a decreased activity following MT intervention (Malisza et al., 2003b).
Other variables like expectations, psychosocial factors, the therapeutic alliance between patient and clinician, and placebo may influence the effectiveness of MT (Kalauokalani et al., 2001, Williams et al., 2007, Fuentes et al., 2014).
Particularly, the patient's expectation on a given kind of intervention may be more important on the outcome than the actual intervention applied: therefore, it is essential to consider the patient's expectation and preferences when deciding which techniques is better for him, as identifying individuals which are more likely to respond seems to be the most important factor (Bishop et al., 2013, Kent et al., 2005).
MT may help in desensitizing the CNS, through exposures to nonthreatening mechanical stimuli, and through patient education, possible helping modulation the pain sensitization (Nijs et al., 2011).

However the individual and relative roles of the different interventions are not knows in details as randomized controlled trials are lacking.
A better understanding of the mechanisms is essential for identifying patients likely to respond to MT, and in order to provide a greater acceptance of MT by healthcare providers (Wahner-Roedler et al., 2006).

5.3 MT and exercises in neck pain

As neck pain is a common complain, many subjects search for conservative treatments such as MT and exercises for pain relief.
MT and exercises are often used as options in the treatment of neck pain, and different reviews support their effectiveness (Bronfort et al., 2004, Gross et al., 2004), also in specific groups of neck pain, as WAD and MNP (Miller et al., 2010, Kay et al., 2012).
This literature shows evidence of reduction of pain and disability, and improvement in overall quality of life with MTs in neck pain patients (Bronfort et al., 2004, Gross et al., 2004).
However, inclusion criteria, methodological quality, pain duration, and outcomes assessment are often very various (Sarigiovannis & Hollis, 2005).
This may at least partially explain why still no consensus exists to which approach is the best to manage neck pain patients, but a combination of MT and exercises seems to give the best clinical outcomes, as reported by another systematic review (Macaulay et al., 2007).
In fact, also a recent systematic review, reported that no conclusion regarding the type of MT techniques can be drawn yet (Voogt et al., 2015).
It is clearly emerging the need of profiling subjects according to prognostic factors, in order to give the appropriate therapy to specific sub-groups of neck pain subjects: for example, those at high risk of poor recovery may need a more variated approach from those at low risk of poor recovery.
On the other hand, too intensive multimodal approach may have iatrogenic effects, reinforcing beliefs of having something serious and which can't be easily solved.
A Cochrane review concluded that manipulation and mobilization produces similar changes (Gross et al., 2010): in study II, spinal mobilization was included but not spinal manipulation, as its clinical effects seems to be similar but with lesser risk for the vertebral artery, and it is a technique well accepted by all patients.
A recent update from the same group, concluded that specific strengthening exercises of the neck, scapulothoracic and shoulder are beneficial for chronic neck pain patients, but again, the optimal dosage is still unclear (Gross et al., 2016).

However, specific exercises must be tailored, as general exercise doesn't seem to help in long-term for pain and disability in WAD subjects (Griffin et al., 2017).
To nowdays, which is the best exercise approach in chronic WAD (Ludvigsson et al., 2015) and chronic MNP (Evans et al., 2012) is still controversial.
Furthermore, different factors (pain intensity, disability, phase of neck pain and muscle function) may influence the response to exercise.
For example, in the first phase low load exercise are usually choosen, as they are safe and must be pain-free, as pain has an immediate effect on muscle function (Cagnie et al., 2011).
In neck pain subjects, changes in sensorimotor function are commonly found, and may include: delayed activation of deep muscles with postural perturbation (Falla et al., 2004a), reduced specifity of sternocleidomastoid muscles (Falla et al., 2010), muscle fibers changes (Uhlig et al., 1995), reduced smoothness of movement (Grip et al., 2008), and decreased muscle cross-sectional area and fatty infiltration (Elliott et al., 2011).
In the first stages, these modification may reflect an attempt of the CNS to protect the painful/injured region from further damage or pain (Hodges et al., 2003).
Of particular relevance are deep cervical flexors (i.e. longus colli and longus capitis), which have shown impaired activation in people with neck pain (Falla et al., 2004b). These muscles are usually assessed through the cranio-cervical flexion test (Jull et al., 2008), which has shown content validity and reliability (Jørgensen et al., 2014).
These dysfunctions have been found among different chronic neck pain populations: in subjects with cervicogenic headache (Jull et al., 2007b), with WAD (Sterling et al., 2003b), with non-specific neck pain (Jull et al., 2004), and with occupational factors (Johnston et al., 2008b).
These muscles have an important role in supporting the cervical posture, due to their role in segmental stability which is not accomplished when only large superficial muscles (i.e. sternocleidomastoid and anterior scalene muscles) are active (Vasavada et al., 1998).
It has been recently confirmed that sternocleidomastoid and anterior scalene muscles iperactivity is an indicator of reduced activity of the deep cervical flexors during cranio-cervical flexion test (Jull and Falla, 2016).
Confirming this idea, it has been shown that subjects with chronic neck pain have a reduced ability to maintain a good sitting posture during a distracting task when compared to healthy subjects, and a re-training program of the deep muscles demonstrated a significant improvement in maintaining a good sitting posture (improvement not found in patients performing a conventional endurance-strength training of the cervical flexors muscles) (Falla et al., 2007).

Retraining the deep cervical flexors has a positive effect in reducing neck symptoms (Falla et al., 2012, Falla et al., 2013, Almaz Abdel-aziem and Hussin Draz, 2016), and improve deep flexors activation (Jull et al., 2009), but the effect on improvement in PPTs levels is controversial (Izquierdo et al., 2016, Lluch et al., 2013).

On the other hand, a 12 weeks exercise programme (craniocervical flexion training, neck extensor training, scapular training, posture re-education, and sensorimotor exercises) did not provide additional benefit on pain intensity over advice alone in chronic WAD subjects (Michaleff et al., 2014).

Because no clear evidence of which MT and exercise combinations gives the best clinical outcomes, in paper II it was investigated the response to a multimodal therapeutic protocol for subjects with WAD and MNP (six sessions in total).

It is necessary to remind that when applying a protocol involving different techniques is hard to identify which one of the techniques has been more useful in terms of improvement.

In paper II, every session lasted 30 minutes, and included soft tissue techniques (IC of TrPs), spinal mobilization, muscle energy techniques, manual traction, and specific cervical spine exercise (retraction and deep neck flexors retraining).

TrPs treatment (IC) was applied to active TrPs in the suboccipital, upper trapezius, levator scapulae, and sternocleidomastoid muscle bilaterally, with the diagnosis performed as described by Simons (1999).

The technique was maintained for every muscle until the subject reported a decrease of pain of around 50%, and in any case never more than two minutes (Cagnie et al., 2013, Aguilera et al., 2009).

Then, as the upper trapezius is usually the muscle most affected by TrPs in individuals with neck pain (Chiarotto et al., 2016), muscle energy technique was applied over this muscle bilaterally, as described by Nagrale et al., 2010.

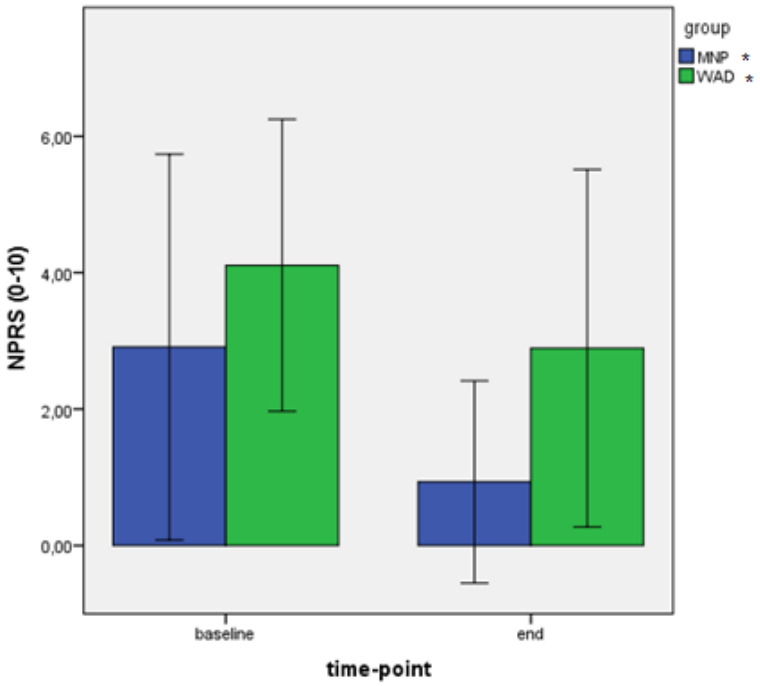
Spinal mobilization (grade III-IV central posterior-anterior) was performed on each spinal process from T4 to C3 for 30 seconds in each level (Maitland, 1983), followed by a light manual intermittent traction for two minutes (Jellad et al., 2009).

Finally, subjects were instructed about how to perform home exercises consisting in cranio-cervical flexion training targeting deep neck flexors (i.e. longus colli and longus capitis), and retraction exercise, both performed 4-5 times a day with 10 repetitions on each session.

At the end of every MT session subjects were asked to perform both exercise, and if the therapist noted an improvement (consisting in less fatigue, less compensatory movement, better quality of movement, or less activation of the superficial muscles in the deep neck flexor exercise), subjects were asked to raise the duration of every single repetitions to 5 or 10 seconds holds.

In fact, low load exercise has been proven to produce an hypoalgesic effects greater than higher load exercise (O'Leary et al., 2007), while progressing to greater load targets more strength and resistance to fatigue (O'Leary et al., 2012).
This was a standardized protocol, but specific exercises need to be individually tailored, as "one size fits all" approach to exercise may not be adequate, but the choice of exercises must be drive by the assessment to identify the physical features that are likely to be related to the patient's symptoms, in order to get the best improvement (Falla and Hodges, 2017).
The main objective of paper II was not to propose a new protocol for treatment of neck pain subjects, but to establish if a different response to MT and exercises may be expected and if so if this could be related to different degree of sensitization.
In fact, when altered central pain processing is present, this could limit the effectiveness of therapeutic exercises, and CS should be addressed before or in combination with exercises (Nijs et al., 2015).
Results from paper II showed that WAD subjects at baseline exhibited higher neck-related disability ($P=0.021$), larger pain areas ($P=0.003$) and lower PPTs in the tibialis anterior muscle ($P=0.009$) than those with MNP (**Table 2**), which can be all considered related to higher sensitization levels (Johnston et al., 2008a, O'Neill et al., 2007, Fernández-Carnero et al., 2009).
Nevertheless, surprisingly this did not influence the response to MT intervention, with both groups showing similar improvements for all clinical outcomes (pain intensity, neck-related disability, pain area extension) (all, $P<0.01$).
Figures 9,10, and 11 shows the mean of pain intensity, neck-related disability, and pain area extension in both groups, at baseline and after the six sessions of MT (end).

Figure 9. NPRS improvement with MT treatment in both groups (data from paper II)



NPRS: numeric pain rating scale; MNP: mechanical neck pain; WAD: whiplash-associated disorders.

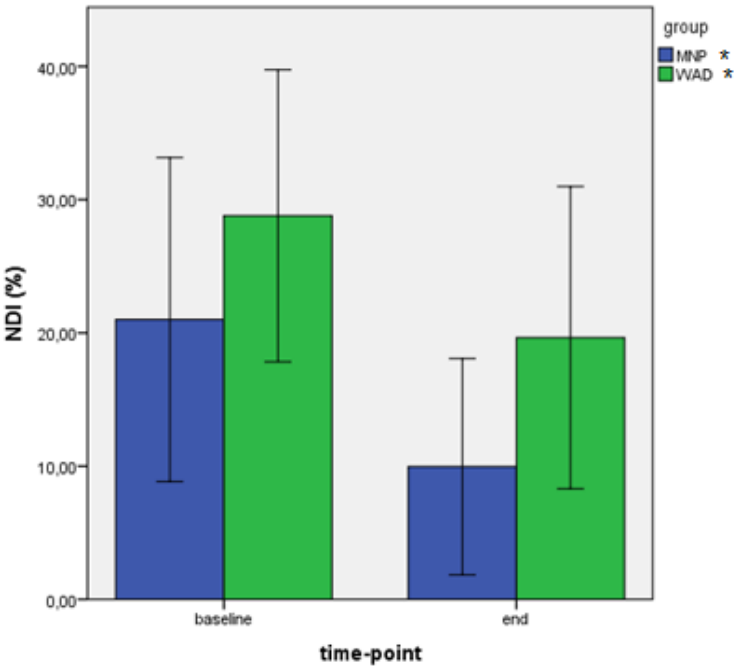
Data are expressed as mean ± standard deviation (95% confidence interval).

*Significant differences (P<0.05) between baseline and end time-points in NPRS values.

It has been previously found that subjects with chronic WAD and signs of sensitization, showed minimal improvement (Jull et al., 2007a): the different treatment approach used in the present paper, difference in the neck pain population may explain these findings which could lead to different conclusions.
Furthermore, no significant changes in PPTs levels were found in the two groups (both, P>0.222), informing that the proposed MT protocol alone is not enough to provoke a change in widespread pressure pain hypersensitivity (i.e. increasing PPTs), suggesting that a multimodal approach may be required.
These findings suggest that CS may be present at different degrees in subjects from both groups, but this does not seems to limit the clinical improvements (in subjects

with a mean level of pain and disability), although this approach alone seems to be non sufficient to provoke an improvement in PPTs and that therapeutic approaches targeting also CNS hyperexcitability are needed.

Figure 10. NDI improvement with MT treatment in both groups (data from paper II)



NPRS: numeric pain rating scale; MNP: mechanical neck pain; WAD: whiplash-associated disorders.

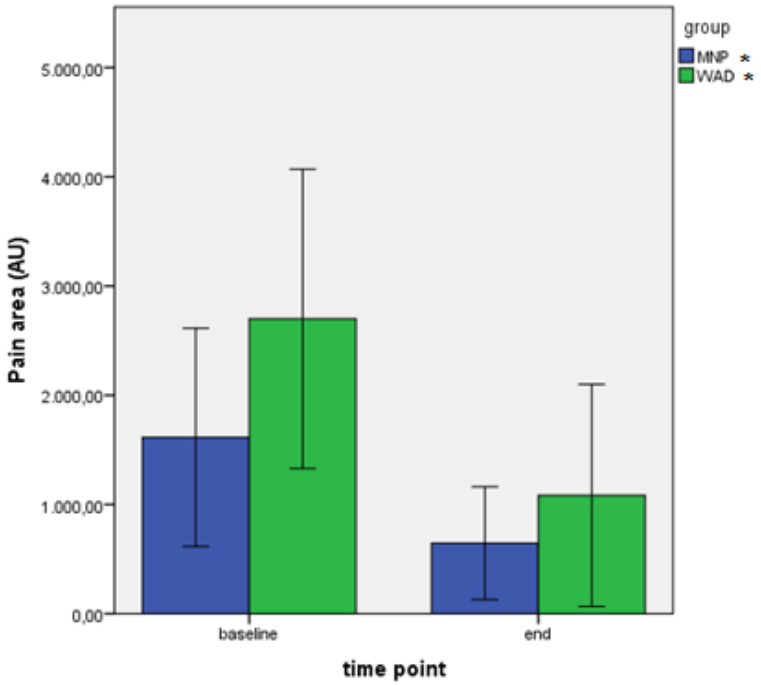
Data are expressed as mean ± standard deviation (95% confidence interval).

*Significant differences (P<0.05) between baseline and end time-points in NDI values.

A greater sample size would have allowed to create sub-group of subjects from both groups with the greatest signs of CS; this could help to understand if the level of CS may be the key for recognizing which subjects may show the best response to MT treatment, for both clinical and psychophysical outcomes, and thus allowing to profile neck pain subjects who will be responders or not responders to conservative treatment.

In conclusion, these results support that neck pain subjects may benefit from MT and exercises (as previously reported in many papers), regardless of neck pain origin, but if CS is present in some subjects, these may require a multimodal approach targeting also the CNS. Neck pain subjects may improve in clinical outcomes with MT and exercises, despite not having a reduction of CS: it is an important finding which suggest that if CS remains a feature of these improved subjects, this may be a possible explanation for the typical course of many chronic neck pain subjects with aggravation and remission.

Figure 11. Pain area improvement with MT treatment in both groups (data from paper II)



NPRS: numeric pain rating scale; MNP: mechanical neck pain; WAD: whiplash-associated disorders.

Data are expressed as mean ± standard deviation (95% confidence interval).

*Significant differences (P<0.05) between baseline and end time-points in pain area values.

6. LIMITATIONS OF THE STUDIES

The first limitation is that a control group of healthy subjects has not been included in the studies. This limit the generalizability of our findings, as it can't be excluded that healthy subjects may present some of the same characteristics.
Sample size did not allow sub-group analysis: this would help to identify which subjects are more sensitized in both groups, and which characteristics may be related to the degree of sensitization (e.g. physical characteristics, number of TrPs, clinical presentation, response to treatment, health status).
Further, the informations regarding CS were obtained only with PPTs assessment and clinical investigation, but other features could be investigated with more QST and give a more complete picture (e.g. thermal pain thresholds, conditioning pain modulation, nociception flexor reflex) of central pain processing alterations.
Pressure algometry may not sufficiently assess sensitivity of deep tissues (as also superficial tissues are stimulated) and central nervous system hypersensitivity.
In the same way, the physical examination did not include ROM measurement, which is commonly reduced in neck pain (Spitzer et al., 1995;,Treleaven, 2008), but has shown to be an inconsistent factor in the prognosis of neck pain (Walton et al., 2013).
In paper III and IV, TrPs have been investigated only in upper trapezius muscles; although the result support the importance of active TrPs on sensitization, assessing more muscles may help in having better informations on the role of TrPs on sensitization (and spatial summation phenomenon).
Paper IV supported the importance of time in the spreading of sensitization: but the study had a cross-sectional design, while longitudinal studies would help in understand the transition from localized to widespread sensitization.
Different medical conditions or different medication may have a different importance in pain sensitization: specific statistical analysis for different medication and different medical conditions may help in determining if some of them may be more implicated in the sensitization process.
Finally, psychological aspects are often present in neck pain subjects (especially in WAD subjects) and may have an influence on the clinical presentation and outcomes of rehabilitation, as they likely interact with other aspects of the clinical picture and may play a role in the symptoms experience. An exploration of the psychological aspects was out of the scope of this project and for that reason has not been investigated.
At this stage, selection bias (chronic neck pain searching for treatment in the symptomatic phase) may limit the clinical relevance of the present findings and it's generalizability to all neck pain population, and further studies are needed.

7. CONCLUSIONS

The result of the present project support the importance of TrPs in neck pain subjects, as they can be part of the sensitization process, and they are relevant in both WAD and MNP subjects, although WAD subjects showed a higher prevalence of active TrPs.
It is necessary to identify neck pain subjects with the greater signs of sensitization, regardless the cause of neck pain: in fact, even if MNP subjects shows less signs of CS, some individuals of this group may be characterized by a sensitization of the pain system, requiring an adequate treatment.
Further, the associations between clinical and psychophysical outcomes were similar in the two groups, and they does not seem to be influenced by the pathogenesis of neck pain.
MT seems to produce similar effects on improving pain and disability, but not helping in decreasing widespread pressure pain hypersensitivity, which may need to be addressed with central-aging treatments and not only from the periphery.
The present findings suggest that the health status may influence the intensity of pain sensitization, and it should be investigated in neck pain subjects.
Particularly the duration of health status complaints seems to be an important factor, related to the degree of widespread pressure pain hypersensitivity.
On conclusion, profiling subjects with neck pain may help in finding the better therapeutic option for every single subjects regardless the origin of neck pain, as sensitization may be present also in some individuals with MNP, and they need to be clinically identified.
In fact, the most sensitized subjects may rapidly improve in the short term with MT and exercises, but this improvement in clinical outcomes may not be accompanied by a reduction of CS, which may possibly represent one of the mechanism for the cyclic pain suffered from many chronic neck pain subjects.

8. FUTURE DIRECTIONS

According to the findings presented in this thesis, future research could be directed towards profiling and phenotyping neck pain patients based on sensitization parameters.
The present studies suggest that CS features may be present in both traumatic and non-traumatic neck pain subjects, and this should be further investigated in longitudinal studies for understanding the time course of CS development and progression, as the time may play a very important role in the progression of sensitization.
Also the role of health status on sensitization needs to be investigated in more details and in longitudinal studies, with focus on which specific medication or medical conditions, which may add individually to the sensitization processes.
An aspect not investigated in this thesis is the role of psychological factors: depression, mood disorders, anxiety should also be investigated in future research as may be present in neck pain subjects and have a relationship with the sensitization progression.
Other future aspects not yet investigated, as genetic factors, should be studied as they may help understanding why CS may develop easily and/or faster in some patients.
A model targeting the periphery (like done in paper II) may help in reducing the peripheral nociceptive input, but a multimodal study in which the most sensitized subjects receive also specific centrally-acting medication or psychological intervention may provide additional clinical information improving the management of the most sensitized neck pain subjects, and possibly avoid such a high rate of chronicity of neck pain.

9. PERSONAL REFLECTIONS

Managing a PhD project in the last years together with my daily clinical activity has been very stimulating and challenging at the same time.
Translating evidence from scientific research into clinical practice is not always an easy process, as the two worlds are often more distant they should be.
Lack of time, routine intervention, patient habits, physical therapist habits, are all factors that may complicate this translational process.
Nevertheless, from a clinical point of view, this project consistently changed the way I work with the day-to-day treatment of neck pain patients.
The first main change is due to the huge amount of scientific papers that opened my mind (from the more theoretical to the more practical ones). Being constantly updated on the recent literature about the clinical problems that you deal with everyday in the clinical setting should be mandatory, but in reality it is not so easy and always possible to stay updated.
The result is being more confident in what I do, in the way I apply clinical reasoning, in the way I interact with patients, and finally on the techniques I apply.
Furthermore, giving information to the patient about the latest research results, their dysfunctions, their treatment, and their prognosis, is for sure a procedure that gave me more credibility: talking of my own research project, immediately makes me an "expert" of that specific field for the patients.
This brings many patients easier and faster into a therapeutic alliance, and thereby increasing the chances of obtaining good outcomes.
The medical history investigation and the assessment procedure has consistently changed compared to few years ago: our findings supported how important is to understanding if the patient sitting in front of you has CS features or not. This may help in the decisional process of which could be the best therapy, if other treatments and professional figures are needed, and in formulating an idea on the outcome.
Information about the general health status (medication, medical condition, surgical operation, musculoskeletal pain) are now always investigated in more details, as they may reveal information about the sensitization.
Furthermore, the studies have strengthened my TrPs assessment in neck pain patients, as our findings support the importance of TrPs in neck pain patients, and their treatment may substantially influence the final outcome being active TrPs associated with widespread pressure pain hypersensitivity.
At the same time the findings have suggested that often CS patients may clinically show improvement (as happened in study II), but this may not necessarily reflects in lowering CS levels, and this explained me why so many patients with neck pain have such high recurrence rate.

REFERENCES

Affaitati, G., Costantini, R., Fabrizio, A., Lapenna, D., Tafuri, E., & Giamberardino, M.A. (2011). Effects of treatment of peripheral pain generators in fibromyalgia patients. *European Journal of Pain*, *15*(1), 61–69. http://doi.org/10.1016/j.ejpain.2010.09.002

Aguilera, F.J.M., Martín, D.P., Masanet, R.A., Botella, A.C., Soler, L.B., & Morel, F.B. (2009). Immediate Effect of Ultrasound and Ischemic Compression Techniques for the Treatment of Trapezius Latent Myofascial Trigger Points in Healthy Subjects: A Randomized Controlled Study. *Journal of Manipulative and Physiological Therapeutics*, *32*(7), 515–520. http://doi.org/10.1016/j.jmpt.2009.08.001

Almaz Abdel-aziem, A., Hussin Draz, A., Elzaiat Street, A., & Elsaryat, B. (2016). Efficacy of deep neck flexor exercise for neck pain: a randomized controlled study. *Turk J Phys Med Rehab*, *6262*(2). http://doi.org/10.5606/tftrd.2016.84565

Angst, M.S., & Clark, J.D. (2006). Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*, *104*(3), 570–87. http://www.ncbi.nlm.nih.gov/pubmed/16508405

Annaswamy, T.M., De Luigi, A.J., O'Neill, B.J., Keole, N., & Berbrayer, D. (2011). Emerging Concepts in the Treatment of Myofascial Pain: A Review of Medications, Modalities, and Needle-based Interventions. *PM&R*, *3*(10), 940–961. http://doi.org/10.1016/j.pmrj.2011.06.013

Antonaci, F., Sand, T., & Lucas, G.A. (1998). Pressure algometry in healthy subjects: inter-examiner variability. *Scand J Rehabil Med 1998*; 30(1):3-8.

Apkarian, A.V., Baliki, M.N., & Geha, P.Y. (2009). Towards a theory of chronic pain. *Progress in Neurobiology*, *87*(2), 81–97. http://doi.org/10.1016/j.pneurobio.2008.09.018

Aranda-Villalobos, P., Navarro-Espigares, J.L., Villalobos, M., Arendt-Nielsen, L., & Arroyo-morales, M. (2013). Normalization of Widespread Pressure Pain Hypersensitivity After Total Hip Replacement in Patients With Hip Osteoarthritis Is Associated With Clinical and Functional Improvements. *Arthritis Reum, 65*(5), 1262–1270. http://doi.org/10.1002/art.37884

Arendt-Nielsen, L., Egsgaard, L.L., Petersen, K.K., Eskehave, T.N., Graven-Nielsen, T., Hoeck, H.C., & Simonsen, O. (2015). A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different

disease stages and pain levels. *European Journal of Pain*, *19*(10), 1406–1417. http://doi.org/10.1002/ejp.651

Arendt-Nielsen, L., Madsen, H., Jarrell, J., & Gregersen, H. (2014). Pain evoked by distension of the uterine cervix in women with dysmenorrhea: evidence for central sensitization. *Acta Obstet Gynecol Scand*, *93*, 741–748. http://doi.org/10.1111/aogs.12403

Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H., & Graven-Nielsen, T. (2010) Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. http://doi.org/10.1016/j.pain.2010.04.003

Arendt-Nielsen, L., & Yarnitsky, D. (2009). Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. *The Journal of Pain, 10*(6), 556–572. http://doi.org/10.1016/j.jpain.2009.02.002

Ashina, S., Bendtsen, L., Ashina, M., Magerl, W., Jensen, R., & Ashina, S. (2006). Generalized hyperalgesia in patients with chronic tension-type headache. *Cephalalgia*, 26(8):940-8. https://www.researchgate.net/profile/Walter_Magerl/publication/6899752_Generalized_Hyperalgesia_in_Patients_With_Chronic_Tension-Type_Headache/links/54b522070cf26833efd06c7a.pdf

Ballyns, J.J., Shah, J.P., Hammond, J., Gebreab, T, Gerber, L.H., & Sikdar, S. (2011). Objective sonographic measures for characterizing myofascial trigger points associated with cervical pain. *Journal of Ultrasound in Medicine : Official Journal of the American Institute of Ultrasound in Medicine, 30*(10), 1331–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21968483

Banic, B., Petersen-Felix, S., Andersen, O.K., Radanov, B.P., Villiger, P.M., Arendt-Nielsen, L., & Curatolo, M. (2004). Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain*, *107*(1-2), 7–15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14715383

Baron, R., Hans, G., & Dickenson, A. H. (2013). Peripheral Input and Its Importance for Central Sensitization. *Annals of Neurology*, 74(5):630-636.http://doi.org/10.1002/ana.24017

Basmajian, J.V. & Nyberg, R. (1993). *Rational manual therapies*. Baltimore: Williams & Wilkins. Retrieved from http://lib.ugent.be/en/catalog/rug01:000287469

Benyamin, R. M., Singh, V., Parr, A. T., Conn, A., Diwan, S., & Abdi, S. (2009). Systematic review of the effectiveness of cervical epidurals in the

management of chronic neck pain. *Pain Physician*, 12(1), 137–57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19165300

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E., & George, S. Z. (2009). The mechanisms of manual therapy in the treatment of musculoskeletal pain: A comprehensive model. *Manual Therapy*, *14*(5), 531–538. http://doi.org/10.1016/j.math.2008.09.001

Bishop, M. D., Beneciuk, J. M., & George, S. Z. (2011). Immediate reduction in temporal sensory summation after thoracic spinal manipulation. *The Spine Journal : Official Journal of the North American Spine Society*, *11*(5), 440–6. http://doi.org/10.1016/j.spinee.2011.03.001

Bishop, M. D., Mintken, P., Bialosky, J. E., & Cleland, J. A. (2013). Patient Expectations of Benefit From Interventions for Neck Pain and Resulting Influence on Outcomes. *Journal of Orthopaedic & Sports Physical Therapy*, *43*(7), 457–465. http://doi.org/10.2519/jospt.2013.4492

Blanpied, P. R., Gross, A. R., Elliott, J. M., Devaney, L. L., Clewley, D., Walton, D. M., … Robertson, E. K. (2017). Neck Pain: Revision 2017. *Journal of Orthopaedic & Sports Physical Therapy*, 47(7), A1–A83. http://doi.org/10.2519/jospt.2017.0302

Bogduk, N. (1999). The neck. *Best Practice & Research Clinical Rheumatology*, *13*(2), 261–285. http://doi.org/10.1053/berh.1999.0020

Borghouts, J. A. ., Koes, B. W., Vondeling, H., & Bouter, L. M. (1999). Cost-of-illness of neck pain in The Netherlands in 1996. *Pain*, *80*(3), 629–636. http://doi.org/10.1016/S0304-3959(98)00268-1

Bot, S. D. M., van der Waal, J. M., Terwee, C. B., van der Windt, D. A. W. M., Scholten, R. J. P. M., Bouter, L. M., & Dekker, J. (2005). Predictors of outcome in neck and shoulder symptoms: a cohort study in general practice. *Spine*, *30*(16), E459–70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16103840

Bouwense, S. A., Ali, U. A., Broek, R. P., Issa, Y., Eijck, C. H. Van, & Goor, H. Van. (2013). Altered central pain processing after pancreatic surgery for chronic pancreatitis. *Br J Surg,* 100(13): 1797–1804. http://doi.org/10.1002/bjs.9322

Boyles, R., Fowler, R., Ramsey, D., & Burrows, E. (2015). Effectiveness of trigger point dry needling for multiple body regions: a systematic review. *The Journal of Manual & Manipulative Therapy*, 23(5), 276–93. http://doi.org/10.1179/2042618615Y.0000000014

Bron, C., Franssen, J., Wensing, M., & Oostendorp, R. A. B. (2007). Interrater reliability of palpation of myofascial trigger points in three shoulder muscles. *The Journal of Manual & Manipulative Therapy,* 15(4), 203–15. http://doi.org/10.1179/106698107790819477

Bron, C., de Gast, A., Dommerholt, J., Stegenga, B., Wensing, M., & Oostendorp, R. A. (2011). Treatment of myofascial trigger points in patients with chronic shoulder pain: a randomized, controlled trial. *BMC Medicine*, *9*(1), 8. http://doi.org/10.1186/1741-7015-9-8

Bronfort, G., Haas, M., Evans, R. L., & Bouter, L. M. (2004). Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. *The Spine Journal*, *4*(4), 335–356. http://doi.org/10.1016/j.spinee.2003.06.002

Cagnie, B., Castelein, B., Pollie, F., Steelant, L., Verhoeyen, H., & Cools, A. (2015). Evidence for the Use of Ischemic Compression and Dry Needling in the Management of Trigger Points of the Upper Trapezius in Patients with Neck Pain. *American Journal of Physical Medicine & Rehabilitation*, *94*(7), 573–583. http://doi.org/10.1097/PHM.0000000000000266

Cagnie, B., Dewitte, V., Coppieters, I., Oosterwijck, J. Van, Cools, A., & Danneels, L. (2013). Effect of ischemic compression on trigger points in the neck and shoulder muscles in office workers: a cohort study. *J Manipulative Physiol Ther*, 36(8):482-9. http://doi.org/10.1016/j.jmpt.2013.07.001

Cagnie, B., Dhooge, F., Van Akeleyen, J., Cools, A., Cambier, D., & Danneels, L. (2012). Changes in microcirculation of the trapezius muscle during a prolonged computer task. *European Journal of Applied Physiology*, 112(9), 3305–3312. http://doi.org/10.1007/s00421-012-2322-z

Cagnie, B., Dirks, R., Schouten, M., Parlevliet, T., Cambier, D., & Danneels, L. (2011). Functional reorganization of cervical flexor activity because of induced muscle pain evaluated by muscle functional magnetic resonance imaging. *Manual Therapy*, 16(5), 470–475. http://doi.org/10.1016/j.math.2011.02.013

Carnes, D., Mars, T. S., Mullinger, B., Froud, R., & Underwood, M. (2010). Adverse events and manual therapy: A systematic review. *Manual Therapy*, *15*(4), 355–363. http://doi.org/10.1016/j.math.2009.12.006

Carroll, L. J., Hogg-Johnson, S., Côté, P., van der Velde, G., Holm, L. W., Carragee, E. J., … Haldeman, S. (2008). Course and Prognostic Factors for Neck Pain in Workers. *European Spine Journal*, *17*(S1), 93–100. http://doi.org/10.1007/s00586-008-0629-6

Carroll, L. J., Holm, L. W., Hogg-Johnson, S., Côtè, P., Cassidy, J. D., Haldeman, S., … Guzman, J. (2009). Course and Prognostic Factors for Neck Pain in Whiplash-Associated Disorders (WAD). *Journal of Manipulative and Physiological Therapeutics*, *32*(2), S97–S107. http://doi.org/10.1016/j.jmpt.2008.11.014

Carstensen, T. B. W., Frostholm, L., Oernboel, E., Kongsted, A., Kasch, H., Jensen, T. S., & Fink, P. (2008). Post-trauma ratings of pre-collision pain and psychological distress predict poor outcome following acute whiplash trauma: A 12-month follow-up study. *Pain*, 139(2), 248–259. http://doi.org/10.1016/j.pain.2008.04.008

Chaiamnuay, P., Darmawan, J., Muirden, K. D., & Assawatanabodee, P. (1998). Epidemiology of rheumatic disease in rural Thailand: a WHO-ILAR COPCORD study. Community Oriented Programme for the Control of Rheumatic Disease. *The Journal of Rheumatology*, *25*(7), 1382–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9676773

Chaibi, A., & Russell, M. B. (2012). Manual therapies for cervicogenic headache: a systematic review. *The Journal of Headache and Pain*, 13(5), 351–359. http://doi.org/10.1007/s10194-012-0436-7

Chesterton, L. S., Sim, J., Wright, C. C., & Foster, N. E. (2007). Interrater Reliability of Algometry in Measuring Pressure Pain Thresholds in Healthy Humans, Using Multiple Raters. *The Clinical Journal of Pain*, *23*(9), 760–766. http://doi.org/10.1097/AJP.0b013e318154b6ae

Chiarotto, A., Clijsen, R., Fernández-de-Las-Peñas, C., & Barbero, M. (2016). Prevalence of Myofascial Trigger Points in Spinal Disorders: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, *97*(2), 316–337. http://doi.org/10.1016/j.apmr.2015.09.021

Chien, A., & Sterling, M. (2010). Sensory hypoaesthesia is a feature of chronic whiplash but not chronic idiopathic neck pain. *Manual Therapy*, *15*(1), 48–53. http://doi.org/10.1016/j.math.2009.05.012

Childs, J. D., Cleland, J. A., Elliott, J. M., Teyhen, D. S., Wainner, R. S., Whitman, J. M., … Torburn, L. (2011). Neck Pain: Clinical Practice Guidelines Linked to the International Classification of Functioning, Disability, and Health From the Orthopaedic Section of the American Physical Therapy Association. *Journal of Women's Health Physical Therapy,* 35(2), 57–90. http://doi.org/10.1097/JWH.0b013e3182267762

Chou, L.-W., Kao, M.-J., & Lin, J.-G. (2012). Probable mechanisms of needling therapies for myofascial pain control. *Evidence-Based Complementary and Alternative Medicine: eCAM*, *2012*, 705327.

http://doi.org/10.1155/2012/705327

Cleland, J. A., Childs, J. D., & Whitman, J. M. (2008). Psychometric Properties of the Neck Disability Index and Numeric Pain Rating Scale in Patients With Mechanical Neck Pain. *Archives of Physical Medicine and Rehabilitation*, *89*(1), 69–74. http://doi.org/10.1016/j.apmr.2007.08.126

Cleland, J. A., Glynn, P., Whitman, J. M., Eberhart, S. L., MacDonald, C., & Childs, J. D. (2007). Short-Term Effects of Thrust Versus Nonthrust Mobilization/Manipulation Directed at the Thoracic Spine in Patients With Neck Pain: A Randomized Clinical Trial. *Physical Therapy*, *87*(4), 431–440. http://doi.org/10.2522/ptj.20060217

Colloca, C. J., Keller, T. S., Harrison, D. E., Moore, R. J., Gunzburg, R., & Harrison, D. D. (2006). Spinal manipulation force and duration affect vertebral movement and neuromuscular responses. *Clinical Biomechanics*, *21*(3), 254–262. http://doi.org/10.1016/j.clinbiomech.2005.10.006

Coppieters, I., Cagnie, B., Danneels, L., Ickmans, K., & Meeus, M. (2015). Central pain modulation and cognitive functioning in patients with traumatic and non-traumatic chronic neck pain: preliminary results. *EFIC 2015 Abstracts*. Retrieved from https://biblio.ugent.be/publication/6925652

Coronado, R. A., Simon, C. B., Valencia, C., & George, S. Z. (2014). Experimental pain responses support peripheral and central sensitization in patients with unilateral shoulder pain. *The Clinical Journal of Pain*, *30*(2), 143–51. http://doi.org/10.1097/AJP.0b013e318287a2a4

Côté, P., Cassidy, D. J., Carroll, L. J., & Kristman, V. (2004). The annual incidence and course of neck pain in the general population: a population-based cohort study. *Pain*, *112*(3), 267–273. http://doi.org/10.1016/j.pain.2004.09.004

Côté, P., Cassidy, J. D., & Carroll, L. (2003). The epidemiology of neck pain: what we have learned from our population-based studies. *The Journal of the Canadian Chiropractic Association*, *47*(4), 284. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504974/

Côté, P., Hogg-Johnson, S., Cassidy, J. D., Carroll, L., Frank, J. W., & Bombardier, C. (2007). Early aggressive care and delayed recovery from whiplash: Isolated finding or reproducible result? *Arthritis & Rheumatism*, 57(5), 861–868. http://doi.org/10.1002/art.22775

Côté, P., van der Velde, G., David Cassidy, J., Carroll, L. J., Hogg-Johnson, S., Holm, L. W., … Peloso, P. M. (2008). The Burden and Determinants of Neck Pain in Workers. *European Spine Journal*, *17*(S1), 60–74. http://doi.org/10.1007/s00586-008-0626-9

Côté, P., Wong, J. J., Sutton, D., Shearer, H. M., Mior, S., Randhawa, K., … Salhany, R. (2016). Management of neck pain and associated disorders: A clinical practice guideline from the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *European Spine Journal*, *25*(7), 2000–2022. http://doi.org/10.1007/s00586-016-4467-7

Curatolo, M. (2011b). Diagnosis of Altered Central Pain Processing. *Spine*, *36*(25 Suppl), S200–S204. http://doi.org/10.1097/BRS.0b013e3182387f3d

Curatolo, M., Arendt-nielsen, L., & Petersen-felix, S. (2006). Central Hypersensitivity in Chronic Pain: Mechanisms and Clinical Implications. *Phys Med Rehabil Clin N Am, 17*(2):287–302. http://doi.org/10.1016/j.pmr.2005.12.010

Curatolo, M., Bogduk, N., Ivancic, P. C., McLean, S. A., Siegmund, G. P., & Winkelstein, B. A. (2011a). The role of tissue damage in whiplash-associated disorders: discussion paper 1. *Spine*, *36*(25 Suppl), S309–15. http://doi.org/10.1097/BRS.0b013e318238842a

Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L., Giani, C., Zbinden, A. M., & Radanov, B. P. (2001). Central hypersensitivity in chronic pain after whiplash injury. *The Clinical Journal of Pain*, *17*(4), 306–15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11783810

De Meulemeester, K. E., Castelein, B., Coppieters, I., Barbe, T., Cools, A., & Cagnie, B. (2017). Comparing Trigger Point Dry Needling and Manual Pressure Technique for the Management of Myofascial Neck/Shoulder Pain: A Randomized Clinical Trial. *Journal of Manipulative and Physiological Therapeutics*, *40*(1), 11–20. http://doi.org/10.1016/j.jmpt.2016.10.008

Descalzi, G., Ikegami, D., Ushijima, T., Nestler, E. J., Zachariou, V., & Narita, M. (2015). Epigenetic mechanisms of chronic pain. *Trends in Neurosciences*, *38*(4), 237–246. http://doi.org/10.1016/j.tins.2015.02.001

Desmeules, J. A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P., … Vischer, T. L. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism*, *48*(5), 1420–1429. http://doi.org/10.1002/art.10893

Dommerholt, J. (2005). Persistent Myalgia Following Whiplash. *Curr Pain Headache Rep,* 9(5):326-30.

Drewes, M.A., Pedersen, J., Reddy, H., Rasmussen, K., Funch-Jensen, P., Arendt-Nielsen, L. & Gregersen, H. (2006) Central sensitization in patients with non-cardiac chest pain: A clinical experimental study. *Scandinavian Journal of Gastroenterology,* 41(6), 640–649.

http://doi.org/10.1080/00365520500442559

Dundar, U., Evcik, D., Samli, F., Pusak, H., & Kavuncu, V. (2007). The effect of gallium arsenide aluminum laser therapy in the management of cervical myofascial pain syndrome: a double blind, placebo-controlled study. *Clinical Rheumatology*, *26*(6), 930–934. http://doi.org/10.1007/s10067-006-0438-4

Ehrmann Feldman, D., Shrier, I., Rossignol, M., & Abenhaim, L. (2002). Risk factors for the development of neck and upper limb pain in adolescents. *Spine*, *27*(5), 523–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11880838

Elliott, J., Pedler, A., Kenardy, J., Galloway, G., Jull, G., & Sterling, M. (2011). The temporal development of fatty infiltrates in the neck muscles following whiplash injury: an association with pain and posttraumatic stress. *PloS One*, 6(6), e21194. http://doi.org/10.1371/journal.pone.0021194

Espí-López, G. V., Arnal-Gómez, A., Arbós-Berenguer, T., González, Á. A. L., & Vicente-Herrero, T. (2014). Effectiveness of Physical Therapy in Patients with Tension-type Headache: Literature Review. *Journal of the Japanese Physical Therapy Association = Rigaku Ryoho*, *17*(1), 31–8. http://doi.org/10.1298/jjpta.17.31

Ettlin, T., Schuster, C., Stoffel, R., Brüderlin, A., & Kischka, U. (2008). A Distinct Pattern of Myofascial Findings in Patients After Whiplash Injury. *Archives of Physical Medicine and Rehabilitation*, *89*(7), 1290–1293. http://doi.org/10.1016/j.apmr.2007.11.041

Evans, R., Bronfort, G., Schulz, C., Maiers, M., Bracha, Y., Svendsen, K., … Transfeldt, E. (2012). Supervised Exercise With and Without Spinal Manipulation Performs Similarly and Better Than Home Exercise for Chronic Neck Pain. *Spine*, 37(11), 903–914. http://doi.org/10.1097/BRS.0b013e31823b3bdf

Evers, S., & Marziniak, M. (2010). Clinical features , pathophysiology , and treatment of medication-overuse headache. *The Lancet Neurology*, *9*(4), 391–401. http://doi.org/10.1016/S1474-4422(10)70008-9

Falla, D., & Hodges, P. W. (2017). Individualized Exercise Interventions for Spinal Pain. *Exerc Sport Sci Rev*, 45(2):105–115. http://doi.org/10.1249/JES.0000000000000103

Falla, D., Jull, G., & Hodges, P. W. (2004a). Feedforward activity of the cervical flexor muscles during voluntary arm movements is delayed in chronic neck pain. *Experimental Brain Research*, 157(1), 43–48. http://doi.org/10.1007/s00221-003-1814-9

Falla, D. L., Jull, G. A., & Hodges, P. W. (2004b). Patients With Neck Pain Demonstrate Reduced Electromyographic Activity of the Deep Cervical Flexor Muscles During Performance of the Craniocervical Flexion Test. *Spine*, *29*(19), 2108–2114. http://doi.org/10.1097/01.brs.0000141170.89317.0e

Falla, D., Jull, G., Russell, T., Vicenzino, B., & Hodges, P. (2007). Effect of Neck Exercise on Sitting Posture in Patients With Chronic Neck Pain. *Physical Therapy*, *87*(4), 408–417. http://doi.org/10.2522/ptj.20060009

Falla, D., Lindstrøm, R., Rechter, L., Boudreau, S., & Petzke, F. (2013). Effectiveness of an 8-week exercise programme on pain and specificity of neck muscle activity in patients with chronic neck pain: A randomized controlled study. *European Journal of Pain,* 17(10), n/a–n/a. http://doi.org/10.1002/j.1532-2149.2013.00321.x

Falla, D., Lindstrøm, R., Rechter, L., & Farina, D. (2010). Effect of pain on the modulation in discharge rate of sternocleidomastoid motor units with force direction. *Clinical Neurophysiology*, 121(5), 744–753. http://doi.org/10.1016/j.clinph.2009.12.029

Falla, D., O'Leary, S., Farina, D., & Jull, G. (2012). The Change in Deep Cervical Flexor Activity After Training Is Associated With the Degree of Pain Reduction in Patients With Chronic Neck Pain. *The Clinical Journal of Pain*, 28(7), 628–634. http://doi.org/10.1097/AJP.0b013e31823e9378

Farasyn, A., & Meeusen, R. (2005). The influence of non-specific low back pain on pressure pain thresholds and disability. *European Journal of Pain*, *9*(4), 375–375. http://doi.org/10.1016/j.ejpain.2004.09.005

Fejer, R., & Leboeuf-Yde, C. (2012). Does back and neck pain become more common as you get older? A systematic literature review. *Chiropractic & Manual Therapies*, 20(1), 24. http://doi.org/10.1186/2045-709X-20-24

Fernández-Carnero, J., Fernández-de-las-Peñas, C., de la Llave-Rincón, A. I., Ge, H.-Y., & Arendt-Nielsen, L. (2008). Bilateral Myofascial Trigger Points in the Forearm Muscles in Patients With Chronic Unilateral Lateral Epicondylalgia. *The Clinical Journal of Pain*, *24*(9), 802–807. http://doi.org/10.1097/AJP.0b013e31817bcb79

Fernández-Carnero, J., Fernández-de-las-Peñas, C., de la Llave-Rincón, A. I., Ge, H.-Y., & Arendt-Nielsen, L. (2009). Widespread Mechanical Pain Hypersensitivity as Sign of Central Sensitization in Unilateral Epicondylalgia. *The Clinical Journal of Pain*, *25*(7), 555–561. http://doi.org/10.1097/AJP.0b013e3181a68a040

Fernández-de-Las-Peñas, C. (2009). Interaction between Trigger Points and Joint

Hypomobility: A Clinical Perspective. *The Journal of Manual & Manipulative Therapy*, *17*(2), 74–7. http://doi.org/10.1179/106698109790824721

Fernández-de-Las-Peñas, C., Alonso-Blanco, C., Cuadrado, M. L., Gerwin, R. D., & Pareja, J. A. (2006). Trigger Points in the Suboccipital Muscles and Forward Head Posture in Tension-Type Headache. *Headache: The Journal of Head and Face Pain*, *46*(3), 454–460. http://doi.org/10.1111/j.1526-4610.2006.00288.x

Fernández-de-las-Peñas, C., Alonso-Blanco, C., & Miangolarra, J. C. (2007a). Myofascial trigger points in subjects presenting with mechanical neck pain: A blinded, controlled study. *Manual Therapy*, *12*(1), 29–33. http://doi.org/10.1016/j.math.2006.02.002

Fernández-de-las-Peñas, C., Benito-González, E., Palacios-Ceña, M., Wang, K., Castaldo, M., & Arendt-Nielsen, L. (2017). Identification of subgroups of patients with tension type headache with higher widespread pressure pain hyperalgesia. *The Journal of Headache and Pain*, *18*(1), 43. http://doi.org/10.1186/s10194-017-0751-0

Fernández-de-las-Peñas, C., Cuadrado, M.L., Simons, D.G., & Pareja, J.A. (2007c). Myofascial trigger points and sensitization : an updated pain model for tension-type headache. *Cephalalgia,* 27(5):383-93. http://doi.org/10.1111/j.1468-2982.2007.01295

Fernández-de-las-Peñas, C., Galán-del-Río, F., Alonso-Blanco, C., Jiménez-García, R., Arendt-Nielsen, L., & Svensson, P. (2010). Referred Pain from Muscle Trigger Points in the Masticatory and Neck-Shoulder Musculature in Women With Temporomandibular Disoders. *The Journal of Pain*, *11*(12), 1295–1304. http://doi.org/10.1016/j.jpain.2010.03.005

Fernández-de-las-Peñas, C., Ge, H.-Y., Arendt-Nielsen, L., Cuadrado, M. L., & Pareja, J. A. (2007b). The Local and Referred Pain From Myofascial Trigger Points in the Temporalis Muscle Contributes to Pain Profile in Chronic Tension-type Headache. *The Clinical Journal of Pain*, *23*(9), 786–792. http://doi.org/10.1097/AJP.0b013e318153496a

Fernández-Lao, C., Cantarero-Villanueva, I., Fernández-de-las-Peñas, C., Del-Moral-Ávila, R., Menjón-Beltrán, S., & Arroyo-Morales, M. (2011). Widespread Mechanical Pain Hypersensitivity as a Sign of Central Sensitization after Breast Cancer Surgery: Comparison between Mastectomy and Lumpectomy. *Pain Medicine*, *12*(1), 72–78. http://doi.org/10.1111/j.1526-4637.2010.01027.x

Ferrari, A., Baraldi, C., & Sternieri, E. (2015). Medication overuse and chronic migraine: a critical review according to clinical pharmacology. *Expert Opinion*

on Drug Metabolism & Toxicology, *11*(7), 1127–1144. http://doi.org/10.1517/17425255.2015.1043265

Ferrari, R., & Russell, A. S. (1997). The whiplash syndrome--common sense revisited. *The Journal of Rheumatology*, 24(4), 618–23. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9101489

Ferrari, R., & Russell, A. S. (2003). Regional musculoskeletal conditions: neck pain. Best Practice & Research. *Clinical Rheumatology*, 17(1), 57–70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12659821

Ferrari, R., Russell, A. S., Carroll, L. J., & Cassidy, J. D. (2005). A re-examination of the whiplash associated disorders (WAD) as a systemic illness. *Annals of the Rheumatic Diseases*, 64(9), 1337–42. http://doi.org/10.1136/ard.2004.034447

Fingleton, C., Smart, K., Moloney, N., Fullen, B. M., & Doody, C. (2015). Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(7), 1043–1056. http://doi.org/10.1016/j.joca.2015.02.163

Finocchietti, S., Mørch, C. D., Arendt-Nielsen, L., & Graven-Nielsen, T. (2011b). Effects of Adipose Thickness and Muscle Hardness on Pressure Pain Sensitivity. *The Clinical Journal of Pain*, *27*(8), 735–745. http://doi.org/10.1097/AJP.0b013e31820c5353

Finocchietti, S., Nielsen, M., Mørch, C. D., Arendt-Nielsen, L., & Graven-Nielsen, T. (2011a). Pressure-induced muscle pain and tissue biomechanics: A computational and experimental study. *European Journal of Pain*, 15(1), 36–44.

Fredin, K., & Lorås, H. (2017). Manual therapy, exercise therapy or combined treatment in the management of adult neck pain – A systematic review and meta-analysis. *Musculoskeletal Science and Practice*, *31*, 62–71. http://doi.org/10.1016/j.msksp.2017.07.005

Freeman, M. D., Nystrom, A., & Centeno, C. (2009). Journal of Brachial Plexus and Chronic whiplash and central sensitization ; an evaluation of the role of a myofascial trigger points in pain modulation. *Journal of Brachial Plexus and Peripheral Nerve Injury*, 23;4:2. http://doi.org/10.1186/1749-7221-4-2

Fuentes, J., Armijo-Olivo, S., Funabashi, M., Miciak, M., Dick, B., Warren, S., … Gross, D. P. (2014). Enhanced Therapeutic Alliance Modulates Pain Intensity and Muscle Pain Sensitivity in Patients With Chronic Low Back Pain: An Experimental Controlled Study. *Physical Therapy*, *94*(4), 477–489. http://doi.org/10.2522/ptj.20130118

Gautam, M., Benson, C. J., & Sluka, K. A. (2010). Increased response of muscle sensory neurons to decreases in pH after muscle inflammation. *Neuroscience*, *170*(3), 893–900. http://doi.org/10.1016/j.neuroscience.2010.08.003

Ge, H.-Y., Fernández-de-las-peñas, C., & Yue, S. (2011). Myofascial trigger points: spontaneous electrical activity and its consequences for pain induction and propagation. *Chinese Medicine*, *6*(1), 13. http://doi.org/10.1186/1749-8546-6-13

Ge, H.-Y., Nie, H., Madeleine, P., Danneskiold-Samsøe, B., Graven-Nielsen, T., & Arendt-Nielsen, L. (2009). Contribution of the local and referred pain from active myofascial trigger points in fibromyalgia syndrome. *Pain*, *147*(1), 233–240. http://doi.org/10.1016/j.pain.2009.09.019

Gerwin, R.D., Dommerholt J. (1998) Myofascial trigger points in chronic cervical whiplash syndrome. *J Musculoskel Pain,* 6(suppl. 2):28

Gerwin, R. D., Dommerholt, J., & Shah, J. P. (2004). An expansion of Simons' integrated hypothesis of trigger point formation. *Current Pain and Headache Reports*, *8*(6), 468–75. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15509461

Gerwin, R. D., Shannon, S., & Hong, C. (1997). Interrater reliability in myofascial trigger point examination. *Pain*, *69*(1-2): 65–73.

Giamberardino, M. A., Tafuri, E., Savini, A., Fabrizio, A., Affaitati, G., Lerza, R., … Mezzetti, A. (2007). Contribution of Myofascial Trigger Points to Migraine Symptoms. *The Journal of Pain*, *8*(11), 869–878. http://doi.org/10.1016/j.jpain.2007.06.002

Goldsmith, R., Wright, C., Bell, S. F., & Rushton, A. (2012). Cold hyperalgesia as a prognostic factor in whiplash associated disorders: A systematic review. *Manual Therapy*, *17*(5), 402–410. http://doi.org/10.1016/j.math.2012.02.014

Graven-Nielsen, T. (2006). Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. *Scandinavian Journal of Rheumatology*, *35*(sup122), 1–43. http://doi.org/10.1080/03009740600865980

Graven-nielsen, T., & Arendt-nielsen, L. (2010). Assessment of mechanisms in localized and widespread musculoskeletal pain. *Nature Publishing Group*, *6*(10), 599–606. http://doi.org/10.1038/nrrheum.2010.107

Graven-Nielsen, T., Wodehouse, T., Langford, R. M., Arendt-Nielsen, L., & Kidd, B. L. (2012). Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis & Rheumatism*, 64(9), 2907–2916.

http://doi.org/10.1002/art.34466

Griffin, A., Leaver, A., & Moloney, N. (2017). General Exercise Does Not Improve Long-Term Pain and Disability in Individuals With Whiplash-Associated Disorders: A Systematic Review. *Journal of Orthopaedic & Sports Physical Therapy*, *47*(7), 472–480. http://doi.org/10.2519/jospt.2017.7081

Griggs, R. B., Donahue, R. R., Adkins, B. G., Anderson, K. L., Thibault, O., & Taylor, B. K. (2016). Pioglitazone Inhibits the Development of Hyperalgesia and Sensitization of Spinal Nociresponsive Neurons in Type 2 Diabetes. *The Journal of Pain*, *17*(3), 359–373. http://doi.org/10.1016/j.jpain.2015.11.006

Grip, H., Sundelin, G., Gerdle, B., & Stefan Karlsson, J. (2008). Cervical helical axis characteristics and its center of rotation during active head and upper arm movements—comparisons of whiplash-associated disorders, non-specific neck pain and asymptomatic individuals. *Journal of Biomechanics,* 41(13), 2799–2805. http://doi.org/10.1016/j.jbiomech.2008.07.005

Gross, A., Miller, J., Sylva, D. J., Sj, B., Ch, G., Graham, N., … Brønfort, G. (2010). Manipulation or Mobilisation for Neck Pain (Review). *Cochrane Database Syst Rev,* 20;(1):CD004249.

Gross, A. R., Hoving, J. L., Haines, T. A., Goldsmith, C. H., Kay, T., Aker, P., & Bronfort, G. (2004). A Cochrane Review of Manipulation and Mobilization for Mechanical Neck Disorders. *Spine*, *29*(14), 1541–1548. http://doi.org/10.1097/01.BRS.0000131218.35875.ED

Gross, A. R., Paquin, J. P., Dupont, G., Blanchette, S., Lalonde, P., Cristie, T., … Cervical Overview Group. (2016). Exercises for mechanical neck disorders: A Cochrane review update. *Manual Therapy*, *24*, 25–45. http://doi.org/10.1016/j.math.2016.04.005

Guzman, J., Hurwitz, E. L., Carroll, L. J., Haldeman, S., Côté, P., Carragee, E. J., … Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. (2008). A new conceptual model of neck pain: linking onset, course, and care: the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine*, *33*(4 Suppl), S14–23. http://doi.org/10.1097/BRS.0b013e3181643efb

Hains, G., & Hains, F. (2010). Patellofemoral pain syndrome managed by ischemic compression to the trigger points located in the peri-patellar and retro-patellar areas: A randomized clinical trial. *Clinical Chiropractic*, *13*(3), 201–209. http://doi.org/10.1016/j.clch.2010.05.001

Haldeman, S., Carroll, L., & Cassidy, J. D. (2010). Findings From The Bone and Joint Decade 2000 to 2010 Task Force on Neck Pain and Its Associated

Disorders. *Journal of Occupational and Environmental Medicine*, *52*(4), 424–427. http://doi.org/10.1097/JOM.0b013e3181d44f3b

Hanten, W. P., Olson, S. L., Butts, N. L., & Nowicki, A. L. (2000). Effectiveness of a home program of ischemic pressure followed by sustained stretch for treatment of myofascial trigger points. *Physical Therapy*, *80*(10), 997–1003. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11002435

Herren-Gerber, R., Weiss, S., Arendt-Nielsen, L., Petersen-Felix, S., Stefano, G. Di, Radanov, B. P., & Curatolo, M. (2004). Modulation of Central Hypersensitivity by Nociceptive Input in Chronic Pain After Whiplash Injury. *Pain Medicine*, *5*(4), 366–376. http://doi.org/10.1111/j.1526-4637.2004.04055.x

Herzog, W., Kats, M., & Symons, B. (2001). The effective forces transmitted by high-speed, low-amplitude thoracic manipulation. *Spine*, *26*(19), 2105–10; discussion 2110–1. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11698887

Herzog, W., Scheele, D., & Conway, P. J. (1999). Electromyographic responses of back and limb muscles associated with spinal manipulative therapy. *Spine*, *24*(2), 146–52; discussion 153. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9926385

Hidalgo-Lozano, A., Fernández-de-las-Peñas, C., Alonso-Blanco, C., Ge, H.-Y., Arendt-Nielsen, L., & Arroyo-Morales, M. (2010). Muscle trigger points and pressure pain hyperalgesia in the shoulder muscles in patients with unilateral shoulder impingement: a blinded, controlled study. *Experimental Brain Research*, *202*(4), 915–925. http://doi.org/10.1007/s00221-010-2196-4

Ho, K.-Y., & Tan, K.-H. (2007). Botulinum toxin A for myofascial trigger point injection: A qualitative systematic review. *European Journal of Pain*, *11*(5), 519–527. http://doi.org/10.1016/j.ejpain.2006.09.002

Hodges, P. W., Moseley, G. L., Gabrielsson, A., & Gandevia, S. C. (2003). Experimental muscle pain changes feedforward postural responses of the trunk muscles. *Experimental Brain Research,* 151(2), 262–271. http://doi.org/10.1007/s00221-003-1457-x

Hogg-Johnson, S., van der Velde, G., Carroll, L. J., Holm, L. W., Cassidy, J. D., Guzman, J., … Peloso, P. (2008). The Burden and Determinants of Neck Pain in the General Population. *European Spine Journal*, *17*(S1), 39–51. http://doi.org/10.1007/s00586-008-0624-y

Hoheisel, U., Koch, K., & Mense, S. (1994). Functional reorganization in the rat dorsal horn during an experimental myositis. *Pain*, *59*(1), 111–8. Retrieved

from http://www.ncbi.nlm.nih.gov/pubmed/7854791

Hoheisel, U., Mense, S., Simons, D. G., & Yu, X. M. (1993). Appearance of new receptive fields in rat dorsal horn neurons following noxious stimulation of skeletal muscle: a model for referral of muscle pain? *Neuroscience Letters*, *153*(1), 9–12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8510831

Hong, C.-Z., Chen, Y.-N., Twehous, D., & Hong, D. H. (1996). Pressure Threshold for Referred Pain by Compression on the Trigger Point and Adjacent Areas. *Journal of Musculoskeletal Pain*, 4(3), 61–79. http://doi.org/10.1300/J094v04n03_07

Hong, C. Z., & Simons, D. G. (1998). Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. *Archives of Physical Medicine and Rehabilitation*, *79*(7), 863–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9685106

Hoy, D., March, L., Woolf, A., Blyth, F., Brooks, P., Smith, E., … Buchbinder, R. (2014). The global burden of neck pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(7), 1309–1315. http://doi.org/10.1136/annrheumdis-2013-204431

Hsieh, C.-Y. J., Adams, A. H., Tobis, J., Hong, C.-Z., Danielson, C., Platt, K., … Rubel, A. (2002). Effectiveness of four conservative treatments for subacute low back pain: a randomized clinical trial. *Spine*, *27*(11), 1142–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12045509

Hubbard, D. R., & Berkoff, G. M. (1993). Myofascial trigger points show spontaneous needle EMG activity. *Spine*, *18*(13), 1803–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8235865

Hübscher, M., Moloney, N., Leaver, A., Rebbeck, T., McAuley, J. H., & Refshauge, K. M. (2013). Relationship between quantitative sensory testing and pain or disability in people with spinal pain—A systematic review and meta-analysis. *Pain*, *154*(9), 1497–1504. http://doi.org/10.1016/j.pain.2013.05.

Ibáñez-García, J., Alburquerque-Sendín, F., Rodríguez-Blanco, C., Girao, D., Atienza-Meseguer, A., Planella-Abella, S., & Fernández-de-las Peñas, C. (2009). Changes in masseter muscle trigger points following strain-counterstrain or neuro-muscular technique. *Journal of Bodywork and Movement Therapies*, *13*(1), 2–10. http://doi.org/10.1016/j.jbmt.2008.03.001

Ibarra, J. M., Ge, H.-Y., Wang, C., Martínez Vizcaíno, V., Graven-Nielsen, T., & Arendt-Nielsen, L. (2011). Latent Myofascial Trigger Points are Associated With an Increased Antagonistic Muscle Activity During Agonist Muscle Contraction. *The Journal of Pain*, *12*(12), 1282–1288.

http://doi.org/10.1016/j.jpain.2011.09.005

Imamura, M., Alfieri, F. M., Filippo, T. R. M., & Battistella, L. R. (2016). Pressure pain thresholds in patients with chronic nonspecific low back pain. *Journal of Back and Musculoskeletal Rehabilitation*, *29*(2), 327–336. http://doi.org/10.3233/BMR-150636

Itoh, K., Hirota, S., Katsumi, Y., Ochi, H., & Kitakoji, H. (2008). Trigger point acupuncture for treatment of knee osteoarthritis--a preliminary RCT for a pragmatic trial. *Acupuncture in Medicine: Journal of the British Medical Acupuncture Society*, *26*(1), 17–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18356795

Izquierdo, T.G., Pecos-Martin, D., Lluch, E.G., Plaza-Manzano, G., Caldentey, R.R.,Melus, R.R., … Falla, D. (2016). Comparison of cranio-cervical flexion training versus cervical proprioception training in patients with chronic neck pain: A randomized controlled clinical trial. *Journal of Rehabilitation Medicine*, *48*(1), 48–55. http://doi.org/10.2340/16501977-2034

Jarrell, J. (2004). Myofascial dysfunction in the pelvis. *Current Pain and Headache Reports*, *8*(6), 452–456. http://doi.org/10.1007/s11916-004-0066-0

Javanshir, K., Ortega-Santiago, R., Mohseni-Bandpei, M. A., Miangolarra-Page, J. C., & Fernández-de-las-Peñas, C. (2010). Exploration of Somatosensory Impairments in Subjects With Mechanical Idiopathic Neck Pain: A Preliminary Study. *Journal of Manipulative and Physiological Therapeutics*, 33(7), 493–499. http://doi.org/10.1016/j.jmpt.2010.08.022

Jellad, A., Ben Salah, Z., Boudokhane, S., Migaou, H., Bahri, I., & Rejeb, N. (2009). The value of intermittent cervical traction in recent cervical radiculopathy. *Annals of Physical and Rehabilitation Medicine*, *52*(9), 638–652. http://doi.org/10.1016/j.rehab.2009.07.035

Jensen, M. P., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: a comparison of six methods. *Pain*, *27*(1), 117–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3785962

Johansen, M. K., Graven-Nielsen, T., Olesen, A. S., & Arendt-Nielsen, L. (1999). Generalised muscular hyperalgesia in chronic whiplash syndrome. *Pain*, *83*(2), 229–234. http://doi.org/10.1016/S0304-3959(99)00106-2

Johnston, V., Jimmieson, N. L., Jull, G., & Souvlis, T. (2008a). Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. *Pain*, *137*(2), 257–265. http://doi.org/10.1016/j.pain.2007.08.037

Johnston, V., Jull, G., Souvlis, T., & Jimmieson, N. L. (2008b). Neck Movement

and Muscle Activity Characteristics in Female Office Workers With Neck Pain. *Spine*, *33*(5), 555–563. http://doi.org/10.1097/BRS.0b013e3181657d0d

Jørgensen, R., Ris, I., Falla, D., & Juul-kristensen, B. (2014). Reliability, construct and discriminative validity of clinical testing in subjects with and without chronic neck pain. *BMC Musculoskeletal Disord*, 4(15):408.

Juhl, G. I., Jensen, T. S., Norholt, S. E., & Svensson, P. (2008). Central sensitization phenomena after third molar surgery: A quantitative sensory testing study. *European Journal of Pain*, *12*(1), 116–127. http://doi.org/10.1016/j.ejpain.2007.04.002

Julien, N., Goffaux, P., Arsenault, P., & Marchand, S. (n.d.). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*, 114(1-2):295-302. http://doi.org/10.1016/j.pain.2004.12.032

Jull, G., Amiri, M., Bullock-Saxton, J., Darnell, R., & Lander, C. (2007b). Cervical Musculoskeletal Impairment in Frequent Intermittent Headache. Part 1: Subjects With Single Headaches. *Cephalalgia*, *27*(7), 793–802. http://doi.org/10.1111/j.1468-2982.2007.01345.x

Jull, G., & Falla, D. (2016). Does increased superficial neck flexor activity in the craniocervical flexion test reflect reduced deep flexor activity in people with neck pain? *Manual Therapy*, *25*, 43–47. http://doi.org/10.1016/j.math.2016.05.336

Jull, G. A., Falla, D., Vicenzino, B., & Hodges, P. W. (2009). The effect of therapeutic exercise on activation of the deep cervical flexor muscles in people with chronic neck pain. *Manual Therapy*, *14*(6), 696–701. http://doi.org/10.1016/j.math.2009.05.004

Jull, G., Kenardy, J., Hendrikz, J., Cohen, M., & Sterling, M. (2013). Management of acute whiplash: A randomized controlled trial of multidisciplinary stratified treatments. *Pain*, 154(9), 1798–1806. http://doi.org/10.1016/j.pain.2013.05.041

Jull, G., Kristjansson, E., & Dall'Alba, P. (2004). Impairment in the cervical flexors: a comparison of whiplash and insidious onset neck pain patients. *Manual Therapy*, *9*(2), 89–94. http://doi.org/10.1016/S1356-689X(03)00086-9

Jull, G. A., O'Leary, S. P., & Falla, D. L. (2008). Clinical Assessment of the Deep Cervical Flexor Muscles: The Craniocervical Flexion Test. *Journal of Manipulative and Physiological Therapeutics*, *31*(7), 525–533. http://doi.org/10.1016/j.jmpt.2008.08.003

Jull, G., Sterling, M., Kenardy, J., & Beller, E. (2007a). Does the presence of

sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? – A preliminary RCT. *Pain*, *129*(1), 28–34. http://doi.org/10.1016/j.pain.2006.09.030

Kaergaard, A., & Andersen, J. H. (2000). Musculoskeletal disorders of the neck and shoulders in female sewing machine operators: prevalence, incidence, and prognosis. *Occupational and Environmental Medicine*, *57*(8), 528–34. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10896959

Kahl, C., & Cleland, J. A. (2005). Visual analogue scale, numeric pain rating scale and the McGill pain Questionnaire: an overview of psychometric properties. *Physical Therapy Reviews*, *10*(2), 123–128. http://doi.org/10.1179/108331905X55776

Kalauokalani, D., Cherkin, D. C., Sherman, K. J., Koepsell, T. D., & Deyo, R. A. (2001). Lessons from a trial of acupuncture and massage for low back pain: patient expectations and treatment effects. *Spine*, *26*(13), 1418–24. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11458142

Kamper, S. J., Maher, C. G., Hush, J. M., Pedler, A., & Sterling, M. (2011). Relationship Between Pressure Pain Thresholds and Pain Ratings in Patients With Whiplash-associated Disorders. *The Clinical Journal of Pain*, *27*(6), 495–501. http://doi.org/10.1097/AJP.0b013e31820e1185

Kasch, H., Qerama, E., Bach, F. W., & Jensen, T. S. (2005). Reduced cold pressor pain tolerance in non-recovered whiplash patients: a 1-year prospective study. *European Journal of Pain*, *9*(5), 561–561. http://doi.org/10.1016/j.ejpain.2004.11.011

Kay, T,M,, Gross, A,, Goldsmith, C.H., Ruthenford, S., Voth, S., Hoving, J.L., … Santaquida, P.L. (2012) Exercises for mechanical neck disorders (Review). *Cochrane Database Syst Rev,15(8)*:CD004250.

Kehlet, H., Jensen, T. S., Woolf, C. J., & Centre, M. (2006). Persistent postsurgical pain: risk factors and prevention. *Lancet*, 13;367(9522):1618-25.

Kelly, J., Ritchie, C., & Sterling, P. M. (2016). *Musculoskelet Sci Pract*, 27:155-164.

Kent, P., Marks, D., Pearson, W., & Keating, J. (2005). Does Clinician Treatment Choice Improve the Outcomes of Manual Therapy for Nonspecific Low Back Pain? A Metaanalysis. *Journal of Manipulative and Physiological Therapeutics*, *28*(5), 312–322. http://doi.org/10.1016/j.jmpt.2005.04.009

Kietrys, D. M., Palombaro, K. M., Azzaretto, E., Hubler, R., Schaller, B., Schlussel, J. M., & Tucker, M. (2013). Effectiveness of Dry Needling for Upper-Quarter Myofascial Pain: A Systematic Review and Meta-analysis. *Journal of*

Orthopaedic & Sports Physical Therapy, *43*(9), 620–634. http://doi.org/10.2519/jospt.2013.4668

Kim, M.-H., Nahm, F. S., Kim, T. K., Chang, M. J., & Do, S.-H. (2014). Comparison of postoperative pain in the first and second knee in staged bilateral total knee arthroplasty: Clinical evidence of enhanced pain sensitivity after surgical injury. *Pain*, *155*(1), 22–27. http://doi.org/10.1016/j.pain.2013.08.027

Kingston, L., Claydon, L., & Tumilty, S. (2014). The effects of spinal mobilizations on the sympathetic nervous system: A systematic review. *Manual Therapy*, *19*(4), 281–287. http://doi.org/10.1016/j.math.2014.04.004

Korthals-de Bos, I. B. C., Hoving, J. L., van Tulder, M. W., Rutten-van Mölken, M. P. M. H., Adèr, H. J., de Vet, H. C. W., … Bouter, L. M. (2003). Cost effectiveness of physiotherapy, manual therapy, and general practitioner care for neck pain: economic evaluation alongside a randomised controlled trial. *BMJ (Clinical Research Ed.)*, *326*(7395), 911. http://doi.org/10.1136/bmj.326.7395.911

Kostopoulos, D., Nelson, A. J., Ingber, R. S., & Larkin, R. W. (2008). Reduction of Spontaneous Electrical Activity and Pain Perception of Trigger Points in the Upper Trapezius Muscle through Trigger Point Compression and Passive Stretching. *Journal of Musculoskeletal Pain*, *16*(4), 266–278. http://doi.org/10.1080/10582450802479594

Kuan, T.-S., Hsieh, Y.-L., Chen, S.-M., Chen, J.-T., Yen, W.-C., & Hong, C.-Z. (2007). The Myofascial Trigger Point Region. *American Journal of Physical Medicine & Rehabilitation*, *86*(3), 183–189. http://doi.org/10.1097/PHM.0b013e3180320ea7

La Touche, R., Fernández-de-las-Peñas, C., Fernández-Carnero, J., Díaz-Parreño, S., Paris-Alemany, A., & Arendt-Nielsen, L. (2010). Bilateral Mechanical-Pain Sensitivity Over the Trigeminal Region in Patients With Chronic Mechanical Neck Pain. *The Journal of Pain*, *11*(3), 256–263. http://doi.org/10.1016/j.jpain.2009.07.003

La Touche, R., Paris-Alemany, A., Hidalgo-Pérez, A., López-de-Uralde-Villanueva, I., Angulo-Diaz-Parreño, S., & Muñoz-García, D. (2017). Evidence for Central Sensitization in Patients with Temporomandibular Disorders: A Systematic Review and Meta-analysis of Observational Studies. *Pain Practice*. http://doi.org/10.1111/papr.12604

Lang, P. M., Schober, G. M., Rolke, R., Wagner, S., Hilge, R., Offenba, M., … Irnich, D. (2006). Sensory neuropathy and signs of central sensitization in patients with peripheral arterial disease. *Pain,* 124(1-2):190–200.

http://doi.org/10.1016/j.pain.2006.04.011

Lartigue, A. M. (2009). Myofascial Pain Syndrome: Treatments. *Journal of Pain & Palliative Care Pharmacotherapy*, *23*(2), 169–170. http://doi.org/10.1080/15360280902901255

Laursen, R. J., Graven-Nielsen, T., Jensen, T. S., & Arendt-Nielsen, L. (1999). The effect of compression and regional anaesthetic block on referred pain intensity in humans. *Pain*, *80*(1-2), 257–63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10204738

Lavelle, E. D., Lavelle, W., & Smith, H. S. (2007). Myofascial Trigger Points. *Anesthesiology Clinics*, *25*(4), 841–851. http://doi.org/10.1016/j.anclin.2007.07.003

Lee, H., Nicholoson, L. L., Adams, R. D., & Bae, S.-S. (2005). Body Chart Pain Location and Side-Specific Physical Impairment in Subclinical Neck Pain. *Journal of Manipulative and Physiological Therapeutics*, *28*(7), 479–486. http://doi.org/10.1016/j.jmpt.2005.07.004

Lee, M., Silverman, S. M., Hansen, H., Patel, V. B., & Manchikanti, L. (2011). A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*, *14*(2), 145–61. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21412369

Li, L., Ge, H., & Yue, S. (2009). Nociceptive and Non-nociceptive Hypersensitivity at Latent Myofascial Trigger Points, *Clin J Pain 25*(2), 132–137.

Lluch, E., Arguisuelas, M. D., Coloma, P. S., Palma, F., Rey, A., & Falla, D. (2013). Effects of Deep Cervical Flexor Training on Pressure Pain Thresholds Over Myofascial Trigger Points in Patients With Chronic Neck Pain. *Journal of Manipulative and Physiological Therapeutics*, *36*(9), 604–611. http://doi.org/10.1016/j.jmpt.2013.08.004

Lluch, E., Nijs, J., De Kooning, M., Van Dyck, D., Vanderstraeten, R., Struyf, F., & Roussel, N. A. (2015). Prevalence, Incidence, Localization, and Pathophysiology of Myofascial Trigger Points in Patients With Spinal Pain: A Systematic Literature Review. *Journal of Manipulative and Physiological Therapeutics*, *38*(8), 587–600. http://doi.org/10.1016/j.jmpt.2015.08.004

Lopez-de-Uralde-Villanueva, I., Beltran-Alacreu, H., Fernandez-Carnero, J., Kindelan-Calvo, P., & La Touche, R. (2016). Widespread Pressure Pain Hyperalgesia in Chronic Nonspecific Neck Pain with Neuropathic Features: A Descriptive Cross-Sectional Study. *Pain Physician*, *19*(2), 77–88. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26815252

Lord, S. M., Barnsley, L., Wallis, B. J., & Bogduk, N. (1996). Chronic cervical

zygapophysial joint pain after whiplash. A placebo-controlled prevalence study. *Spine*, *21*(15), 1737–44; discussion 1744–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8855458

Lucas, K. R., Polus, B. I., & Rich, P. A. (2004). Latent myofascial trigger points: their effects on muscle activation and movement efficiency, *Journal of Bodywork and Movement Therapies,* 8(3):160–166. http://doi.org/10.1016/j.jbmt.2003.12.002

Lucas, N., Macaskill, P., Irwig, L., Moran, R., & Bogduk, N. (2009). Reliability of Physical Examination for Diagnosis of Myofascial Trigger Points. *The Clinical Journal of Pain*, *25*(1), 80–89. http://doi.org/10.1097/AJP.0b013e31817e13b6

Ludvigsson, M. L., Peterson, G., O'Leary, S., Dedering, Å., & Peolsson, A. (2015). The Effect of Neck-specific Exercise With, or Without a Behavioral Approach, on Pain, Disability, and Self-Efficacy in Chronic Whiplash-associated Disorders. *The Clinical Journal of Pain*, 31(4), 294–303. http://doi.org/10.1097/AJP.0000000000000123

Luime, J. J., Koes, B. W., Miedem, H. S., Verhaar, J. A. N., & Burdorf, A. (2005). High incidence and recurrence of shoulder and neck pain in nursing home employees was demonstrated during a 2-year follow-up. *Journal of Clinical Epidemiology*, *58*(4), 407–413. http://doi.org/10.1016/j.jclinepi.2004.01.022

Macaulay, J., Cameron, M., & Vaughan, B. (2007). The effectiveness of manual therapy for neck pain: a systematic review of the literature. *Physical Therapy Reviews*, *12*(3), 261–267. http://doi.org/10.1179/108331907X223038

MacDermid, J. C., Walton, D. M., Avery, S., Blanchard, A., Etruw, E., McAlpine, C., & Goldsmith, C. H. (2009). Measurement Properties of the Neck Disability Index: A Systematic Review. *Journal of Orthopaedic & Sports Physical Therapy*, *39*(5), 400–C12. http://doi.org/10.2519/jospt.2009.2930

Maitland, G. D. (1983). Treatment of the glenohumeral joint by passive movement. *Physiotherapy*, 69(1): 3–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6836050

Malfliet, A., Kregel, J., Cagnie, B., Meeus, M., Danneels, L., Bramer, W. M., & Nijs, J. (2015). Lack of Evidence for Central Sensitization in Idiopathic, Non-Traumatic Neck Pain: A Systematic Review. *Pain Physician*, 18(3): 223–235.

Malisza, K. L., Gregorash, L., Turner, A., Foniok, T., Stroman, P. W., Allman, A.-A., … Wright, A. (2003b). Functional MRI involving painful stimulation of the ankle and the effect of physiotherapy joint mobilization. *Magnetic Resonance Imaging*, *21*(5), 489–96. Retrieved from

http://www.ncbi.nlm.nih.gov/pubmed/12878258

Malisza, K. L., Stroman, P. W., Turner, A., Gregorash, L., Foniok, T., & Wright, A. (2003a). Functional MRI of the rat lumbar spinal cord involving painful stimulation and the effect of peripheral joint mobilization. *Journal of Magnetic Resonance Imaging*, *18*(2), 152–159. http://doi.org/10.1002/jmri.10339

Manchikanti, L., Singh, V., Datta, S., Cohen, S. P., Hirsch, J. A., & American Society of Interventional Pain Physicians. (2009). Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician*, *12*(4), E35–70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19668291

Mariappan, Y. K., Glaser, K. J., & Ehman, R. L. (2010). Magnetic resonance elastography: A review. *Clinical Anatomy*, *23*(5), 497–511. http://doi.org/10.1002/ca.21006

Mayer. J., Kraus, T., & Ochsmann, E. (2012). Longitudinal evidence for the association between work-related physical exposures and neck and/or shoulder complaints: a systematic review. *International Archives of Occupational and Environmental Health, 85*(6), 587–603. http://doi.org/10.1007/s00420-011-0701-0

McLean, S., Naish, R., Reed, L., Urry, S., & Vicenzino, B. (2002). A pilot study of the manual force levels required to produce manipulation induced hypoalgesia. *Clinical Biomechanics (Bristol, Avon)*, *17*(4), 304–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12034124

McPartland, J. M., Giuffrida, A., King, J., Skinner, E., Scotter, J., & Musty, R. E. (2005). Cannabimimetic effects of osteopathic manipulative treatment. The *Journal of the American Osteopathic Association,* 105(6), 283–91. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16118355

McReynolds, T. M., & Sheridan, B. J. (2005). Intramuscular ketorolac versus osteopathic manipulative treatment in the management of acute neck pain in the emergency department: a randomized clinical trial. *The Journal of the American Osteopathic Association*, *105*(2), 57–68. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15784928

Meeus, M., & Nijs, J. (2007). Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clinical Rheumatology*, *26*(4), 465–473. http://doi.org/10.1007/s10067-006-0433-9

Meeus, M., Nijs, J., Van de Wauwer, N., Toeback, L., & Truijen, S. (2008). Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An

experimental study. *Pain*, *139*(2), 439–448. http://doi.org/10.1016/j.pain.2008.05.018

Meeus, M., Vervisch, S., De Clerck, L. S., Moorkens, G., Hans, G., & Nijs, J. (2012b). Central Sensitization in Patients with Rheumatoid Arthritis: A Systematic Literature Review. *Seminars in Arthritis and Rheumatism*, *41*(4), 556–567. http://doi.org/10.1016/j.semarthrit.2011.08.001

Meeus, M., Nijs, J., Hamers, V., Ickmans, K., & Oosterwijck, J. Van. (2012a). The efficacy of patient education in whiplash associated disorders: a systematic review. *Pain Physician*, 15(5), 351–61. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22996847

Mejuto-Vázquez, M. J., Salom-Moreno, J., Ortega-Santiago, R., Truyols-Domínguez, S., & Fernández-de-las-Peñas, C. (2014). Short-Term Changes in Neck Pain, Widespread Pressure Pain Sensitivity, and Cervical Range of Motion After the Application of Trigger Point Dry Needling in Patients With Acute Mechanical Neck Pain: A Randomized Clinical Trial. *Journal of Orthopaedic & Sports Physical Therapy*, *44*(4), 252–260. http://doi.org/10.2519/jospt.2014.5108

Mense, S. (2010). How Do Muscle Lesions such as Latent and Active Trigger Points Influence Central Nociceptive Neurons? *Journal of Musculoskeletal Pain, 18*(4), 348–353. http://doi.org/10.3109/10582452.2010.502621

Mense, S., & Gerwin, R. D. (Eds.). (2010). *Muscle pain: understanding the mechanisms*. Springer Science & Business Media.

Mense, S., Simons, D. G., & Russell, I. J. (2001). *Muscle pain: understanding its nature, diagnosis, and treatment*. Lippincott Williams & Wilkins.

Michaleff, Z. A., Maher, C. G., Lin, C. C., Rebbeck, T., Jull, G., Latimer, J., … Sterling, M. (2014). Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial. *The Lancet*, *384*(9938), 133–141. http://doi.org/10.1016/S0140-6736(14)60457-8

Miller, J., Gross, A., Sylva, J. D., Burnie, S. J., Goldsmith, C. H., Graham, N., … Hoving, J. L. (2010). Manual therapy and exercise for neck pain: A systematic review. *Manual Therapy*, *15*(4), 334–354. http://doi.org/10.1016/j.math.2010.02.007

Monticone, M., Ferrante, S., Vernon, H., Rocca, B., Dal Farra, F., & Foti, C. (2012). Development of the Italian Version of the Neck Disability Index. *Spine*, *37*(17), E1038–E1044. http://doi.org/10.1097/BRS.0b013e3182579795

Moraska, A. F., Hickner, R. C., Kohrt, W. M., & Brewer, A. (2013). Changes in Blood Flow and Cellular Metabolism at a Myofascial Trigger Point With Trigger Point Release (Ischemic Compression): A Proof-of-Principle Pilot Study. *Archives of Physical Medicine and Rehabilitation*, *94*(1), 196–200. http://doi.org/10.1016/j.apmr.2012.08.216

Moraska, A. F., Schmiege, S. J., Mann, J. D., Butryn, N., & Krutsch, J. P. (2017). Responsiveness of Myofascial Trigger Points to Single and Multiple Trigger Point Release Massages. *American Journal of Physical Medicine & Rehabilitation*, 1. http://doi.org/10.1097/PHM.0000000000000728

Moshiree, B., Zhou, Q., Price, D. D., & Verne, G. N. (2006). Central sensitisation in visceral pain disorders. *Gut*, *55*(7), 905–8. http://doi.org/10.1136/gut.2005.078287

Mourão, F.A., Blyth, F. M., & Branco, J. C. (2010). Generalised musculoskeletal pain syndromes. *Best Practice & Research Clinical Rheumatology*, 24, 829–840. http://doi.org/10.1016/j.berh.2010.10.005

Merskey *H,* Bogduk *N. Classification of chronic pain. 2nd ed. Seattle: IASP Press,*1994*. p. 1*

Munksgaard, S. B., Bendtsen, L., & Jensen, R. H. (2013). Modulation of central sensitisation by detoxification in MOH: Results of a 12-month detoxification study. *Cephalalgia*, *33*(7), 444–453. http://doi.org/10.1177/0333102412475235

Myburgh, C., Larsen, A. H., & Hartvigsen, J. (2008). A Systematic, Critical Review of Manual Palpation for Identifying Myofascial Trigger Points: Evidence and Clinical Significance. *Archives of Physical Medicine and Rehabilitation*, *89*(6), 1169–1176. http://doi.org/10.1016/j.apmr.2007.12.033

Nagrale, A. V., Glynn, P., Joshi, A., & Ramteke, G. (2010). The efficacy of an integrated neuromuscular inhibition technique on upper trapezius trigger points in subjects with non-specific neck pain: a randomized controlled trial. *Journal of Manual & Manipulative Therapy*, *18*(1), 37–43. http://doi.org/10.1179/106698110X12595770849605

Nekovarova, T., Yamamotova, A., Vales, K., Stuchlik, A., Fricova, J., & Rokyta, R. (2014). Common mechanisms of pain and depression: are antidepressants also analgesics? *Frontiers in Behavioral Neuroscience*, 8: 99. http://doi.org/10.3389/fnbeh.2014.00099

Nijs, J., Houdenhove, B. Van, & Oostendorp, R. A. B. (2010). Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, *15*(2), 135–

141. http://doi.org/10.1016/j.math.2009.12.001

Nijs, J., Lluch Girbés, E., Lundberg, M., Malfliet, A., & Sterling, M. (2015). Exercise therapy for chronic musculoskeletal pain: Innovation by altering pain memories. *Manual Therapy*, *20*(1), 216–220. http://doi.org/10.1016/j.math.2014.07.004

Nijs, J., Paul van Wilgen, C., Van Oosterwijck, J., van Ittersum, M., & Meeus, M. (2011). How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: Practice guidelines. *Manual Therapy*, *16*(5), 413–418. http://doi.org/10.1016/j.math.2011.04.005

Nijs, J., Torres-cueco, R., Wilgen, C. P. Van, Girbés, E. L., Struyf, F., Roussel, N., … Moloney, N. (2014). Applying Modern Pain Neuroscience in Clinical Practice: Criteria for the Classification of Central Sensitization Pain. *Pain Physician*, 17: 447–457.

Nijs, J., Van Oosterwijck, J., & De Hertogh, W. (2009). Rehabilitation of chronic whiplash: treatment of cervical dysfunctions or chronic pain syndrome? *Clinical Rheumatology*, 28(3), 243–251. http://doi.org/10.1007/s10067-008-1083-x

Nystrom, N. A., & Freeman, M. D. (2017). Central Sensitization Is Modulated Following Trigger Point Anesthetization in Patients with Chronic Pain from Whiplash Trauma. A Double-Blind, Placebo-Controlled, Crossover Study. *Pain Medicine*. http://doi.org/10.1093/pm/pnx014

O 'Leary, S., Falla, D., Hodges, P. W., Jull, G., & Vicenzino, B. (2007). Specific Therapeutic Exercise of the Neck Induces Immediate Local Hypoalgesia. *The Journal of Pain*, 8(11):832-839.http://doi.org/10.1016/j.jpain.2007.05.014

O'Leary, S., Jull, G., Kim, M., Uthaikhup, S., & Vicenzino, B. (2012). Training Mode–Dependent Changes in Motor Performance in Neck Pain. *Archives of Physical Medicine and Rehabilitation,* 93(7), 1225–1233. http://doi.org/10.1016/j.apmr.2012.02.018

O'Neill, S., Manniche, C., Graven-Nielsen, T., & Arendt-Nielsen, L. (2007). Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *European Journal of Pain*, *11*(4), 415–420. http://doi.org/10.1016/j.ejpain.2006.05.009

Ohnmeiss, D. D. (2000). Repeatability of pain drawings in a low back pain population. *Spine*, *25*(8), 980–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10767812

Pato, U., Di Stefano, G., Fravi, N., Arnold, M., Curatolo, M., Radanov, B. P., …

Sturzenegger, M. (2010). Comparison of randomized treatments for late whiplash. *Neurology*, 74(15), 1223–1230. http://doi.org/10.1212/WNL.0b013e3181d8ffe0

Perreault, T., Dunning, J., & Butts, R. (2017). The local twitch response during trigger point dry needling: Is it necessary for successful outcomes? *Journal of Bodywork and Movement Therapies (In Press)*. http://doi.org/10.1016/j.jbmt.2017.03.008

Pool, J. J. M., Ostelo, R. W. J. G., Köke, A. J., Bouter, L. M., & de Vet, H. C. W. (2006). Comparison of the effectiveness of a behavioural graded activity program and manual therapy in patients with sub-acute neck pain: Design of a randomized clinical trial. *Manual Therapy*, *11*(4), 297–305. http://doi.org/10.1016/j.math.2005.07.006

Ramsook, R. R., & Malanga, G. A. (2012). Myofascial Low Back Pain. *Current Pain and Headache Reports*, *16*(5), 423–432. http://doi.org/10.1007/s11916-012-0290-y

Rathbone, A. T. L., Grosman-Rimon, L., & Kumbhare, D. A. (2017). Interrater Agreement of Manual Palpation for Identification of Myofascial Trigger Points. *The Clinical Journal of Pain*, *33*(8), 715–729. http://doi.org/10.1097/AJP.0000000000000459

Rayegani, S. M., Bayat, M., Bahrami, M. H., Raeissadat, S. A., & Kargozar, E. (2014). Comparison of dry needling and physiotherapy in treatment of myofascial pain syndrome. *Clinical Rheumatology*, *33*(6), 859–864. http://doi.org/10.1007/s10067-013-2448-3

Renan-Ordine, R., Alburquerque-SendÍn, F., Rodrigues De Souza, D. P., Cleland, J. A., & Fernández-de-las-PeÑas, C. (2011). Effectiveness of Myofascial Trigger Point Manual Therapy Combined With a Self-Stretching Protocol for the Management of Plantar Heel Pain: A Randomized Controlled Trial. *Journal of Orthopaedic & Sports Physical Therapy*, *41*(2), 43–50. http://doi.org/10.2519/jospt.2011.3504

Rickards, L. D., Thorsen, H., Lonnberg, F., Cuyper, H. J. De, Oostendorp, R. A., Evans, R., & al., et. (2006). The effectiveness of non-invasive treatments for active myofascial trigger point pain: A systematic review of the literature. *International Journal of Osteopathic Medicine*, *9*(4), 120–136. http://doi.org/10.1016/j.ijosm.2006.07.007

Ris, I., Barbero, M., Falla, D., Holst Larsen, M., Nielsen Kraft, M., Søgaard, K., & Juul-Kristensen, B. (2016). The relation between pain extent and quality-of-life, psychological factors and neck function in patients with chronic neck pain. *Manual Therapy*, *25*, e73–e74.

http://doi.org/10.1016/j.math.2016.05.117

Ritchie, C., & Sterling, M. (2016). Recovery Pathways and Prognosis After Whiplash Injury. *Journal of Orthopaedic & Sports Physical Therapy*, *46*(10), 851–861. http://doi.org/10.2519/jospt.2016.6918

Rivner, M. H. (2001). The neurophysiology of myofascial pain syndrome. *Current Pain and Headache Reports*, *5*(5), 432–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11560808

Roach, K. E., Brown, M. D., Dunigan, K. M., Kusek, C. L., & Walas, M. (1997). Test-Retest Reliability of Patient Reports of Low Back Pain. *Journal of Orthopaedic & Sports Physical Therapy*, *26*(5), 253–259. http://doi.org/10.2519/jospt.1997.26.5.253

Rolke, R., Magerl, W., Campbell, K. A., Schalber, C., Caspari, S., Birklein, F., & Treede, R.-D. (2006). Quantitative sensory testing: a comprehensive protocol for clinical trials. *European Journal of Pain*, *10*(1), 77–77. http://doi.org/10.1016/j.ejpain.2005.02.003

Ross, J. K., Bereznick, D. E., & McGill, S. M. (2004). Determining cavitation location during lumbar and thoracic spinal manipulation: is spinal manipulation accurate and specific? *Spine*, *29*(13), 1452–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15223938

Roussel, N. A., Nijs, J., Meeus, M., Mylius, V., Fayt, C., & Oostendorp, R. (2013). Central Sensitization and Altered Central Pain Processing in Chronic Low Back Pain. *The Clinical Journal of Pain*, *29*(7), 625–638. http://doi.org/10.1097/AJP.0b013e31826f9a71

Rozenfeld, E., Finestone, A. S., Moran, U., Damri, E., & Kalichman, L. (2017). Test-retest reliability of myofascial trigger point detection in hip and thigh areas. *Journal of Bodywork and Movement Therapies*. (In Press) http://doi.org/10.1016/j.jbmt.2017.03.023

Ruiz-Sáez, M., Fernández-de-las-Peñas, C., Blanco, C. R., Martínez-Segura, R., & García-León, R. (2007). Changes in Pressure Pain Sensitivity in Latent Myofascial Trigger Points in the Upper Trapezius Muscle After a Cervical Spine Manipulation in Pain-Free Subjects. *Journal of Manipulative and Physiological Therapeutics*, *30*(8), 578–583. http://doi.org/10.1016/j.jmpt.2007.07.014

Sánchez-Jiménez, A., Cantarero-Villanueva, I., Molina-Barea, R., Fernández-Lao, C., Galiano-Castillo, N., & Arroyo-Morales, M. (2014). Widespread Pressure Pain Hypersensitivity and Ultrasound Imaging Evaluation of Abdominal Area after Colon Cancer Treatment. *Pain Medicine*, *15*(2), 233–240.

http://doi.org/10.1111/pme.12281

Sarigiovannis, P., & Hollins, B. (2005). Effectiveness of manual therapy in the treatment of non-specific neck pain: a review. *Physical Therapy Reviews*, *10*(1), 35–50. http://doi.org/10.1179/108331905X43436

Sawynok, J., Esser, M. J., & Reid, A. R. (2001). Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. *Journal of Psychiatry & Neuroscience: JPN*, *26*(1), 21–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11212590

Schellingerhout, J. M., Verhagen, A. P., Heymans, M. W., Koes, B. W., de Vet, H. C., & Terwee, C. B. (2012). Measurement properties of disease-specific questionnaires in patients with neck pain: a systematic review. *Quality of Life Research*, *21*(4), 659–670. http://doi.org/10.1007/s11136-011-9965-9

Sciotti, V. M., Mittak, V. L., DiMarco, L., Ford, L. M., Plezbert, J., Santipadri, E., … Ball, K. (2001). Clinical precision of myofascial trigger point location in the trapezius muscle. *Pain*, *93*(3), 259–66. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11514085

Scott, D., Jull, G., & Sterling, M. (n.d.). Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. *The Clinical Journal of Pain*, *21*(2), 175–81. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15722811

Seferiadis, A., Rosenfeld, M., & Gunnarsson, R. (2004). A review of treatment interventions in whiplash-associated disorders. *European Spine Journal,* 13(5), 387–97. http://doi.org/10.1007/s00586-004-0709-1

Seffinger, M. A., Najm, W. I., Mishra, S. I., Adams, A., Dickerson, V. M., Murphy, L. S., & Reinsch, S. (2004). Reliability of spinal palpation for diagnosis of back and neck pain: a systematic review of the literature. *Spine*, *29*(19), E413–25. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15454722

Shah, J. P., & Gilliams, E. A. (2008). Uncovering the biochemical milieu of myofascial trigger points using in vivo microdialysis: An application of muscle pain concepts to myofascial pain syndrome. *Journal of Bodywork and Movement Therapies*, *12*, 371–384. http://doi.org/10.1016/j.jbmt.2008.06.006

Shah, J. P., Phillips, T. M., Danoff, J. V., & Gerber, L. H. (2005). An in vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. *Journal of Applied Physiology*, *99*(5). Retrieved from http://jap.physiology.org/content/99/5/1977.short

Shah, J. P., Thaker, N., Heimur, J., Aredo, J. V, Sikdar, S., & Gerber, L. (2015).

Myofascial Trigger Points Then and Now: A Historical and Scientific Perspective. *PM&R*, *7*(7), 746–761. http://doi.org/10.1016/j.pmrj.2015.01.024

Sheather-Reid, R. B., & Cohen, M. L. (1998). Psychophysical evidence for a neuropathic component of chronic neck pain. *Pain,* 75(2-3), 341–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9583770

Sikdar, S., Shah, J. P., Gebreab, T., Yen, R.-H., Gilliams, E., Danoff, J., & Gerber, L. H. (2009). Novel Applications of Ultrasound Technology to Visualize and Characterize Myofascial Trigger Points and Surrounding Soft Tissue. *Archives of Physical Medicine and Rehabilitation*, *90*(11), 1829–1838. http://doi.org/10.1016/j.apmr.2009.04.015

Simons D.G. (2004). Review of enigmatic MTrPs as a common cause of enigmatic musculoskeletal pain and dysfunction. *J Electromyogr Kinesiol*, *14*, 95–107. http://doi.org/10.1016/j.jelekin.2003.09.018

Simons, D. G., Travell, J. G., Simons, L. S., & Travell, J. G. (1999). *Travell & Simons' myofascial pain and dysfunction: the trigger point manual*. Philadelphia, PA:Lippincott, Williams & Wilkins.

Skou, S. T., Graven-Nielsen, T., Rasmussen, S., Simonsen, O. H., Laursen, M. B., & Arendt-Nielsen, L. (2013). Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. *Pain*, 154(9): 1588-94. http://doi.org/10.1016/j.pain.2013.04.033

Smart, K. M., Blake, C., Staines, A., Thacker, M., & Doody, C. (2012). Mechanisms-based classifications of musculoskeletal pain: Part 1 of 3: Symptoms and signs of central sensitisation in patients with low back (±leg) pain. *Manual Therapy*, *17*(4), 336–344. http://doi.org/10.1016/j.math.2012.03.013

Smith, A. D., Jull, G., Schneider, G., Frizzell, B., Hooper, R. A., & Sterling, M. (2014). Cervical Radiofrequency Neurotomy Reduces Central Hyperexcitability and Improves Neck Movement in Individuals with Chronic Whiplash. *Pain Medicine*, *15*(1), 128–141. http://doi.org/10.1111/pme.12262

Spitzer, W. O., Skovron, M. L., Salmi, L. R., Cassidy, J. D., Duranceau, J., Suissa, S., & Zeiss, E. (1995). Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine*, *20*(8 Suppl), 1S–73S. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7604354

Srbely, J. Z., Dickey, J. P., Bent, L. R., Lee, D., & Lowerison, M. (2010). Capsaicin-Induced Central Sensitization Evokes Segmental Increases in Trigger Point Sensitivity in Humans. *The Journal of Pain*, *11*(7), 636–643.

http://doi.org/10.1016/j.jpain.2009.10.005

Srbely, J. Z., Dickey, J. P., Lowerison, M., Edwards, M. A., Nolet, P. S., & Wong, L. L. (2008). Stimulation of myofascial trigger points with ultrasound induces segmental antinociceptive effects: A randomized controlled study. *Pain*, *139*(2), 260–266. http://doi.org/10.1016/j.pain.2008.04.009

Srbely, J. Z., Kumbhare, D., & Grosman-Rimon, L. (2016). A narrative review of new trends in the diagnosis of myofascial trigger points: diagnostic ultrasound imaging and biomarkers. *The Journal of the Canadian Chiropractic Association*, *60*(3), 220–225. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27713577

Srikiatkhachorn, A., Tarasub, N., & Govitrapong, P. (2000). Effect of chronic analgesic exposure on the central serotonin system: a possible mechanism of analgesic abuse headache. *Headache*, *40*(5), 343–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10849027

Ståhl, M., Mikkelsson, M., Kautiainen, H., Häkkinen, A., Ylinen, J., & Salminen, J. J. (2004). Neck pain in adolescence. A 4-year follow-up of pain-free preadolescents. *Pain*, *110*(1), 427–431. http://doi.org/10.1016/j.pain.2004.04.025

Staud, R., Craggs, J. G., Robinson, M. E., Perlstein, W. M., & Price, D. D. (2007). Brain activity related to temporal summation of C-fiber evoked pain. *Pain*, *129*(1), 130–142. http://doi.org/10.1016/j.pain.2006.10.010

Sterling, M., Hendrikz, J., Kenardy, J. (2010). Developmental trajectories of pain/disability and PTSD symptoms following whiplash injury. *Pain,* 150(1):22-8.

Sterling, M., Hendrikz, J., Kenardy, J., Kristjansson, E., Dumas, J.-P., Niere, K., … Jull, G. (2012). Assessment and validation of prognostic models for poor functional recovery 12 months after whiplash injury: A multicentre inception cohort study. *Pain*, *153*(8), 1727–1734. http://doi.org/10.1016/j.pain.2012.05.004

Sterling, M., Jull, G., & Kenardy, J. (2006). Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain*, *122*(1), 102–108. http://doi.org/10.1016/j.pain.2006.01.014

Sterling, M., Jull, G., Vicenzino, B., & Kenardy, J. (2003). Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain, 104(3):* 509–517. http://doi.org/10.1016/S0304-3959(03)00078-2

Sterling, M., Jull, G., Vicenzino, B., Kenardy, J., & Darnell, R. (2003).

Development of motor system dysfunction following whiplash injury. *Pain*, *103*(1-2), 65–73. http://doi.org/10.1016/S0304-3959(02)00420-7

Stone, A. M., Vicenzino, B., Lim, E. C. W., & Sterling, M. (2013). Measures of central hyperexcitability in chronic whiplash associated disorder – A systematic review and meta-analysis. *Manual Therapy*, *18*(2), 111–117. http://doi.org/10.1016/j.math.2012.07.009

Sutton, D. A., Côté, P., Wong, J. J., Varatharajan, S., Randhawa, K. A., Yu, H., … Stupar, M. (2016). Is multimodal care effective for the management of patients with whiplash-associated disorders or neck pain and associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *The Spine Journal*, *16*(12), 1541–1565. http://doi.org/10.1016/j.spinee.2014.06.019

Szeto, G. P. Y., Straker, L. M., & O'Sullivan, P. B. (2005). A comparison of symptomatic and asymptomatic office workers performing monotonous keyboard work—2: Neck and shoulder kinematics. *Manual Therapy*, *10*(4), 281–291. http://doi.org/10.1016/j.math.2005.01.005

Teodorczyk-Injeyan, J. A., Injeyan, H. S., & Ruegg, R. (2006). Spinal Manipulative Therapy Reduces Inflammatory Cytokines but Not Substance P Production in Normal Subjects. *Journal of Manipulative and Physiological Therapeutics*, *29*(1), 14–21. http://doi.org/10.1016/j.jmpt.2005.10.002

Toomingas, A. (1999). Characteristics of pain drawings in the neck-shoulder region among the working population. *International Archives of Occupational and Environmental Health*, *72*(2), 98–106. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10197481

Treaster, D., Marras, W. S., Burr, D., Sheedy, J. E., & Hart, D. (2006). Myofascial trigger point development from visual and postural stressors during computer work. *Journal of Electromyography and Kinesiology*, *16*(2), 115–124. http://doi.org/10.1016/j.jelekin.2005.06.016

Treleaven, J. (2008). Sensorimotor disturbances in neck disorders affecting postural stability, head and eye movement control. *Manual Therapy*, 13(1), 2–11. http://doi.org/10.1016/j.math.2007.06.003

Uhlig, Y., Weber, B. R., Grob, D., & Müntener, M. (1995). Fiber compositionand fiber transformations in neck muscles of patients with dysfunction of the cervical spine. *Journal of Orthopaedic Research*, 13(2), 240–249. http://doi.org/10.1002/jor.1100130212

Van Oosterwijck, J., Nijs, J., Meeus, M., & Paul, L. (2013). Evidence for central sensitization in chronic whiplash: A systematic literature review. *European*

Journal of Pain, 17(3), 299–312. http://doi.org/10.1002/j.1532-2149.2012.00193.x

Vasavada, A. N., Li, S., & Delp, S. L. (1998). Influence of muscle morphometry and moment arms on the moment-generating capacity of human neck muscles. *Spine*, *23*(4), 412–22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9516695

Vaughan, K., Darbari, D., Chadwick, K., Seamon, C., Diaw, L., Quinn, M., … Vi, J. T. (2015). B23 Visceral Pain - Gastrointestinal / Abdominal B24 Other. *The Journal of Pain*, *16*(4), S34. http://doi.org/10.1016/j.jpain.2015.01.148

Velde, G. Van Der, Yu, H., Paulden, M., Côté, P., Varatharajan, S., Shearer, H. M., … Taylor-vaisey, A. (2016). Which interventions are cost-effective for the management of whiplash-associated and neck pain-associated disorders? A systematic review of the health economic literature by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *The Spine Journal*, *16*(12), 1582–1597. http://doi.org/10.1016/j.spinee.2015.08.025

Verne, G. N., & Price, D. D. (2002). Irritable bowel syndrome as a common precipitant of central sensitization. *Current Rheumatology Reports*, *4*(4), 322–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12126584

Vernon, H., & Mior, S. (1991). The Neck Disability Index: a study of reliability and validity. *Journal of Manipulative and Physiological Therapeutics*, *14*(7), 409–15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1834753

Vicenzino, B., Collins, D., & Wright, A. (1996). The initial effects of a cervical spine manipulative physiotherapy treatment on the pain and dysfunction of lateral epicondylalgia. *Pain*, *68*(1), 69–74. http://doi.org/10.1016/S0304-3959(96)03221-6

Vicenzino, B., Paungmali, A., Buratowski, S., & Wright, A. (2001). Specific manipulative therapy treatment for chronic lateral epicondylalgia produces uniquely characteristic hypoalgesia. *Manual Therapy*, *6*(4), 205–212. http://doi.org/10.1054/math.2001.0411

Vikat, A., Rimpelä, M., Salminen, J. J., Rimpelä, A., Savolainen, A., & Virtanen, S. M. (2000). Neck or shoulder pain and low back pain in Finnish adolescents. *Scandinavian Journal of Public Health*, *28*(3), 164–73. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11045747

Von Korff, M., Ormel, J., Keefe, F. J., & Dworkin, S. F. (1992). Grading the severity of chronic pain. *Pain*, *50*(2), 133–49. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1408309

Voogt, L., Vries, J. De, Meeus, M., Struyf, F., Meuffels, D., & Nijs, J. (2015). Analgesic effects of manual therapy in patients with musculoskeletal pain : A systematic review. *Manual Therapy*, *20*(2), 250–256. http://doi.org/10.1016/j.math.2014.09.001

Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., … Murray, C. J. L. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1545–1602. http://doi.org/10.1016/S0140-6736(16)31678-6

Wahner-Roedler, D. L., Vincent, A., Elkin, P. L., Loehrer, L. L., Cha, S. S., & Bauer, B. A. (2006). Physicians' Attitudes Toward Complementary and Alternative Medicine and Their Knowledge of Specific Therapies: A Survey at an Academic Medical Center. *Evidence-Based Complementary and Alternative Medicine*, *3*(4), 495–501. http://doi.org/10.1093/ecam/nel036

Wall, P. D., & Woolf, C. J. (1984). Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *The Journal of Physiology*, *356*, 443–58. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6520794

Waller, R., Straker, L., O'Sullivan, P., Sterling, M., & Smith, A. (2015). Reliability of pressure pain threshold testing in healthy pain free young adults. *Scandinavian Journal of Pain*, *9*, 38–41. http://doi.org/10.1016/j.sjpain.2015.05.004

Walsh, R., Kinsella, S., McEvoy, J., Baghban, A. A., Goldenberg, D. L., Gerwin, R., … Skootsky, S. (2016). The intra-rater reliability of locating and measuring the severity of latent trigger points in the quadriceps. *Journal of Bodywork and Movement Therapies*, *15*(0), 385–390. http://doi.org/10.1016/j.jbmt.2016.11.015

Walton, D.M., Kwok, T. S. H., Mehta, S., Loh, E., Smith, A., Elliott, J., … Sterling, M. (2017). Cluster Analysis of an International Pressure Pain Threshold Database Identifies 4 Meaningful Subgroups of Adults With Mechanical Neck Pain. *The Clinical Journal of Pain*, 33(5), 422–428. http://doi.org/10.1097/AJP.0000000000000421

Walton, D.M., MacDermid, J. C., Giorgianni, A. A., Mascarenhas, J. C., West, S. C., & Zammit, C. A. (2013). Risk Factors for Persistent Problems Following Acute Whiplash Injury: Update of a Systematic Review and Meta-analysis. *Journal of Orthopaedic & Sports Physical Therapy*, *43*(2), 31–43. http://doi.org/10.2519/jospt.2013.4507

Walton, D.M., MacDermid, J., Nielson, W., Teasell, R., Chiasson, M., & Brown, L.

(2011). Reliability, Standard Error, and Minimum Detectable Change of Clinical Pressure Pain Threshold Testing in People With and Without Acute Neck Pain. *Journal of Orthopaedic & Sports Physical Therapy*, *41*(9), 644–650. http://doi.org/10.2519/jospt.2011.3666

Wang, Y.-H., Ding, X.-L., Zhang, Y., Chen, J., Ge, H.-Y., Arendt-Nielsen, L., & Yue, S.-W. (2010). Ischemic compression block attenuates mechanical hyperalgesia evoked from latent myofascial trigger points. *Experimental Brain Research*, *202*(2), 265–270. http://doi.org/10.1007/s00221-009-2129-2

Williams, N. H., Hendry, M., Lewis, R., Russell, I., Westmoreland, A., & Wilkinson, C. (2007). Psychological response in spinal manipulation (PRISM): A systematic review of psychological outcomes in randomised controlled trials. *Complementary Therapies in Medicine*, *15*(4), 271–283. http://doi.org/10.1016/j.ctim.2007.01.008

Wong, J. J., Fccs, C., Shearer, H. M., Fccs, C., Mior, S., Jacobs, C., … Taylor-vaisey, A. (2016). Are manual therapies , passive physical modalities , or acupuncture effective for the management of patients with whiplash-associated disorders or neck pain and associated disorders? An update of the Bone and Joint Decade Task Force on Neck Pain and Its . *The Spine Journal* (Vol. 16). Elsevier Inc. http://doi.org/10.1016/j.spinee.2015.08.024

Woodcock, A., Young, E. C., & Smith, J. A. (2010). New insights in cough. *British Medical Bulletin*, 96(1): 61–73. http://doi.org/10.1093/bmb/ldq034

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain,* 152(Supplement), S2–S15. http://doi.org/10.1016/j.pain.2010.09.030

Xu, Y., Ge, H., & Arendt-nielsen, L. (2010). Sustained Nociceptive Mechanical Stimulation of Latent Myofascial Trigger Point Induces Central Sensitization in Healthy Subjects. *The Journal of Pain*, *11*(12), 1348–1355. http://doi.org/10.1016/j.jpain.2010.03.010

Xue, B., Zhang, Z., Johnson, R. F., & Johnson, A. K. (2012). Sensitization of Slow Pressor Angiotensin II (Ang II)–Initiated Hypertension. *Hypertension*, *59*(2). Retrieved from http://hyper.ahajournals.org/content/59/2/459.short

Yunus, M. B. (2007). Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Best Practice & Research Clinical Rheumatology*, *21*(3), 481–497. http://doi.org/10.1016/j.berh.2007.03.006

Zwart, J., Dyb, G., Hagen, K., Svebak, S., & Stovner, L. J. (2004). Analgesic overuse among subjects with headache , neck , and low-back pain. *Neurology,*

62(9): 1540–1544.

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-057-9

AALBORG UNIVERSITY PRESS